Archives of Neurology and Psychiatry

VOLUME 51 MAY 1944 NUMBER 5

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ELECTROMYOGRAPHY AS A METHOD FOR DETERMINATION OF LEVEL OF LESIONS IN THE SPINAL CORD

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Fascicular twitching of muscles, with or without atrophy, may occur at the level of a lesion in the spinal cord when the corresponding region of the anterior horn or the motor roots are involved.[1] Below the level of the lesion hyperactive reflexes and other signs of spasticity are usually present. Both types of signs may be studied by means of electromyography, but an investigation of the fasciculations appears to be of greater localizing value than a study of the abnormal phenomena which result from lesions of the long tracts.

Fascicular twitches are the responses of single motor units to stimuli, arising presumably anywhere along the course of the lower motor neuron.[2] They are accompanied by characteristic action potential discharges, which are best seen in records obtained with coaxial needle electrodes.[3] In examination of patients with manifest muscular twitches, such as those characteristic of progressive muscular atrophy and amyotrophic lateral sclerosis, one sees not infrequently motor unit discharges arising from muscles which are not, or are not yet, clinically involved, in that no twitches are visible, and from muscles prior to the onset of wasting. With this experience in mind, the present investigation was initiated in an attempt to utilize clinical and subclinical signs of motor unit discharge for the purpose of localization of structural lesions of the spinal cord.

METHOD AND MATERIAL

The method consisted of a systematic exploration of a wide range of segments of the spinal cord and their motor roots by means of a search for spontaneous motor unit discharges from relaxed muscles supplied by these segments. The cervical part of the cord, including the first dorsal segment, is represented by the muscles of the neck, the shoulder girdle and the upper extremity. The lumbar and sacral parts of the cord are, similarly, represented by the muscles of the pelvic girdle and those of the lower extremity. The dorsal segments were explored by a study of the long muscles of the back at the levels of the spinous processes of the dorsal vertebrae, usually at a distance of about 4 cm. from the midline.

Records of the action potentials were obtained by use of coaxial needle electrodes from all muscles except for the thenar and hypothenar groups and the intrinsic muscles of the hand. The outer part of the coaxial electrodes was made of a gage 25 hypodermic needle, ¾ inch (1.9 cm.) long, and the center part was a gage 40 copper wire (0.09 mm. in diameter). For the small muscles of the hand, pairs of surface electrodes (solder disks) 2 to 3 mm. in diameter were used.

The instrument used for recording was a six channel, ink-writing oscillograph (made by Mr. Albert Grass). The paper tape was moved at a speed of 6 cm. per second. Details of the technic of recording have been described elsewhere.[4]

The electromyographic method was used in about 50 cases in which disease of the spinal cord was suspected. In 24 cases of this series structural lesions involving definite levels of the cord were subsequently observed at operation (16 cases), in roentgenographic studies (7 cases) or at autopsy (1 case). The accompanying table is a summary of the histories and the clinical, laboratory and electromyographic data in all cases of verified lesions of the cord.

RESULTS

Metastatic carcinoma was observed in 5 cases; meningioma, in 4 cases; and intramedullary glioma, in 3 cases. Neurofibroma, schwannoma and herniated intervertebral disk occurred in 2 cases each. Fracture of a vertebra, Paget's disease (osteitis deformans) of the spinal column, mediastinal tumor invading and destroying verte-

Part of the expenses of this study were defrayed by a grant from the Commonwealth Fund.

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Clinical, Laboratory and Electromyographic Data in Twenty-Four Cases of Lesions of the Spinal Cord

Case No.	Initials, Sex	Age, Yr.	History and Symptoms	Clinical Data	Laboratory Data	Electromyographic Changes	Diagnosis
1	C. M. F	55	Pain in left shoulder and wrist over 2 yr.; paresthesias, weakness and atrophy of left hand	Atrophy, weakness and fasciculations in left arm and wrist, with diminished deep reflexes; increased deep reflexes in both legs	Spinal fluid normal. Roentgenogram negative for lesion. Chronaxia: Neuromuscular degeneration of left thenar and hypothenar muscles evident	Motor unit discharges from flexors of forearm, of left more than of right; and from thenar group of right hand. Level of lesion, C6-D1	Calcified, herniated nucleus pulposus between 7th cervical and 1st dorsal left side, verified by operation
2	M. M. M	26	Progressive weakness of right leg and clumsiness of right hand 2 yr.; loss of temperature sense in left leg 1 yr.; urinary difficulties 9 mo.	Weakness and atrophy in right arm and leg; hyperactive deep reflexes in right arm and leg; fasciculations over right scapula; hypesthesia for pain and temperature up to 5th cervical dermatome	Spinal fluid: Xanthochromia; protein 468 mm./100 cc.; 16 cells per cu. mm.; complete block. Roentgenogram negative for lesion. Myelogram with iodized poppyseed oil: Two stops, one at level of atlas and other at L4/5. Determination (2) of chronaxia: No degeneration in muscles of right arm	Motor unit discharges from trapezius muscle bilaterally and from right triceps. Level, C1-C3 and C6-C7; lower level not explored	Multiple neurofibromas (1) between atlas and axis bilaterally, anteriorly, verified by operation; (2) at L4 and 5, verified by operation
3	G. S. M	25	Weakness and clumsiness of right hand 3 yr.; loss of tactile discrimination in right hand 3 yr.	Weakness, stiffness and clumsiness of right arm; spasticity of right leg; pronounced hyperactive reflexes in both arm and leg on right side; atrophy of trapezius and intrinsic muscles of hand on right side; abolition of vibration and position sense and tactile discrimination in right hand and forearm	Spinal fluid: Partial block; total protein 86 and 76 mg./100 cc. Roentgenogram: Essentially normal. Determination of chronaxia. Upper portion of right trapezius showed deep neuromuscular degeneration; otherwise no evidence of neuromuscular change	Motor unit discharges recorded from trapezius, deltoid, biceps and triceps muscles on right side. Level, C1-C7	Intramedullary tumor, probably spongioblastoma, verified by operation at levels C1-C3
4	C. F. F	74	Pain in back 5 mo.; numbness in legs 2 wk.; weakness of legs 10 days; urinary difficulties 2 days	Flaccid paraparesis with equivocal Babinski sign bilaterally; absence of abdominal reflexes; sensory level for all modalities at 1st lumbar segment	Spinal fluid: Complete block; protein 248 mg./100 cc. Roentgenogram: Marked compression of body of 10th dorsal vertebra	Motor unit discharges recorded from muscles of left side of back at levels of spinous processes of 11th and 12th dorsal vertebrae	Multiple myeloma; myelomalacia observed at segments D12 and L1 at autopsy
5	S. Z. M	60	Urinary difficulties 5 yr.; girdle sensation at level of umbilicus 2 yr.; difficulty in walking, loss of power and numbness of both feet 6-8 wk.; tingling in both feet 4-6 wk.	Pronounced weakness of both legs, especially of left; fasciculations in both gastrocnemius muscles; very hyperactive reflexes in both legs; Babinski sign on left; sensory level for pain and temperature sense at 4th dorsal and for touch and vibration sense at 1st lumbar	Spinal fluid: Complete block; protein 648 mg./100 cc. Roentgenogram: Paget's disease, most evident in 7th and 8th dorsal vertebrae	Motor unit discharge bilaterally at D6 and to less degree at D1	Paget's disease, resulting in compression of cord between 1st and 5th dorsal segments, most pronounced at 2d and 3d dorsal (vertebrae), verified by operation
6	H. C. M	46	Pain in midthorax and right shoulder 2 mo.	No clinical signs except for palpable deformity of 5th dorsal vertebra	Spinal fluid: No definite block; protein 252 and 328 mg./100 cc. Roentgenogram: Old compression fracture of 5th dorsal vertebra	Motor unit discharges bilaterally at D8 (best) to D10 (spinous processes)	Fracture of 5th dorsal vertebra, verified roentgenographically
7	M. T. F	64	Pain in chest below left breast and right scapula 14 mo.; weakness in both legs 5 mo.; numbness of lower part of trunk and legs 4-5 mo.; sphincteric disturbance 2-5 wk.	Weakness and spasticity of both legs, more on left side, with extremely hyperactive deep reflexes and bilateral Babinski sign; sensory level for superficial modalities at 6th dorsal and for vibration sense at 5th to 6th dorsal	Spinal fluid: Partial block; protein 94 mg./100 cc. Roentgenogram: Osteoarthritis of dorsal and lumbar portions of spine	Motor unit discharges recorded between D8 and D11 on left and to less degree between D8 and D10 on right	Meningioma adjacent to the 6th dorsal root and extending both ventrally and dorsally, verified by operation
8	R. F. M	15	Disturbance of gait 2 yr.	Moderate atrophy of right shoulder girdle and arm; no clearcut fasciculations; underactive reflexes in right arm and hyperactive in both legs, with bilateral Babinski sign; hyperpathia between 2d and 5th cervical levels	Spinal fluid: Partial block noted on three occasions; protein 76, 63 and 109 (calculated) mg./100 cc. Myelograms with iodized poppyseed oil: Stop at 5th cervical level (cisternal route)	Motor unit discharges recorded from both trapezius muscles and (?) from right deltoid and biceps muscles. Level, C1-C3 (C1-C6)	Syringomyelic cyst of cervical part of cord, verified at operation up at least to C2 level and down approximately to D2 level

				fasciculations; underactive reflexes in right arm and hyperactive in both legs, with bilateral Babinski sign; hyperpathia between 2d and 5th cervical levels	and 100 (calculated) mg./100 cc. Myelograms with iodized poppyseed oil: Stop at 5th cervical level (cisternal route)	and (?) from right deltoid and biceps muscles. Level, C1-C3 (C1-C6)	tion up at least to C2 level and down approximately to D2 level

Clinical, Laboratory and Electromyographic Data in Twenty-Four Cases of Lesions of the Spinal Cord—Continued

9	H. B. M	61	Weakness and numbness of right arm and hand 5 mo.; pain in left elbow and scapula 1 mo.; wasting of right hand 1 mo.; weakness of both legs and incontinence a few days; weakness of grip in both hands, in rignt more than in left, on day of admission	Atrophy of small muscles of right hand; fasciculations of right shoulder girdle and right arm; deep reflexes of arms moderately, and those of both legs extremely hyperactive, with bilateral Babinski sign; no level of sensory loss	Spinal fluid: Partial block; protein 221 mg./100 cc. Roentgenogram: Compression fracture of 8th dorsal vertebra. Myelogram with iodized poppyseed oil: Shows stop at 1st dorsal level. Chronaxia determinations: Neuromuscular degeneration of small muscles of right hand and of thenar muscles of left hand	Motor unit discharges recorded from right trapezius and right biceps. Level, C1-C6	Meningioma on right side between levels C6 and D1, verified at operation
10	C. C. F	43	Pain in right arm and shoulder 10 mo.; weakness and paresthesias of legs 6 mo.; inability to walk 5½ mo.; sphincteric disturbances 2 mo.	Spastic paraparesis with extremely hyperactive reflexes and bilateral Babinski sign; abdominal reflexes absent; hyperesthesia for touch and pain sense below 2d dorsal and for temperature sense below 4th dorsal segment	Spinal fluid: Complete block; protein 276 mg./100 cc. Roentgenogram: Destruction of body of 1st dorsal vertebra (not collapsed) and some involvement of upper margin of 7th cervical vertebra	Motor unit discharges recorded bilaterally at C7-D6, best at D4 on left	Metastatic carcinoma of body of 1st dorsal and lower part of 7th cervical vertebra
11	J. M. M	21	Intermittent pain in neck 2 yr.; intermittent numbness in left arm 1 yr.; transient "girdle" numbness 1 yr. before admission; numbness and progressive paralysis of right arm 8 mo.; progressive spasm and weakness in both legs 6 wk.; progressive sphincteric disturbance 2 wk.	Rigidity of neck; spastic tetraparesis with moderately overactive reflexes in arms, extremely overactive reflexes in legs; with bilateral Hoffmann and Babinski signs; atrophy of both deltoid muscles; sensory level of all modalities at 4th cervical dermatome	Spinal fluid: Complete block; protein 684 mg./100 cc.; 25 lymphocytes. Roentgenogram: Probably normal. Chronaxia: Slight increase for muscles supplied by ulnar nerve; otherwise normal chronaxia	Motor unit discharges recorded from left deltoid and left biceps; (?) discharges from right deltoid muscle; discharges from extensors of right forearm. Level, C4-C6 on left and C4-C6 on right	Adhesive arachnoiditis with cyst at C4-C5, verified at operation
12	C. S. M	63	Sudden onset of pain and weakness in both legs 5 mo. before admission	Atrophy of both legs, of left more than of right; absence of ankle jerk bilaterally; hyperactivity of all other reflexes on both sides; bilateral Hoffmann sign; sensory changes limited to hyperesthesia to pin prick in posterior part of left thigh	Spinal fluid: No block; protein 318 mg./100 cc. Roentgenogram negative for lesion. Air myelogram showed tumor of spinal cord opposite 5th lumbar vertebra. Chronaxia: Slightly increased for gluteus and quadriceps muscles; no real neuromuscular degeneration revealed	Motor unit discharges recorded bilaterally between L1 and L4; in addition, feeble discharges between L5 and S2 on left	Tumor of cauda equina, cystic schwannoma, originating from left anterior 1st sacral root, adherent to left posterior 1st sacral root and left anterior 2d sacral root; extent 4 cm. and diameter 2 cm.; verified at operation
13	M. B. F	52	Transient pain in left knee 18 mo. before admission; "pulling" sensation in left groin 13 mo.; pain in right thigh 9 mo.; difficulty in walking, heaviness and fatigability 3 mo.	Weakness in both legs, especially in extensors; deep reflexes absent in left leg, and absent or diminished in right leg; questionable Babinski sign on left side; sensory level of hypesthesia at 2d lumbar segment	Spinal fluid: Partial block; xanthochromia; protein approximately 3,400 mg./100 cc. Roentgenogram negative for lesions. Myelogram with iodized poppyseed oil; block at body of 2d lumbar vertebra. Chronaxia normal	Motor unit discharges recorded at D7 and D8; in addition, irregular activity of high amplitude (many units) down to L1	Schwannoma of conus extending to cauda; partly cystic, partially solid; verified at operation
14	C. C. M	44	Pain in right scapula 2 yr., in both arms 10 mo., in back of neck 8 mo., in chest 7 mo.; numbness and weakness of both legs, of right more than of left; difficulty in walking and sphincteric disturbance 3 wk.	Weakness of both arms, of left more than of right; weakness of right leg, with foot drop; occasional fascicular twitches in right arm and shoulder; extremely hyperactive reflexes in all four extremities, on left slightly more than on right, with bilateral Babinski sign; sensory level for superficial modalities (hypesthesia) between 8th cervical and 1st dorsal segments; level for vibratory sense at 2d dorsal	No spinal puncture. Roentgenogram: tumor of upper mediastinum, destroying bodies of 7th cervical and 1st dorsal vertebrae and lamina of 1st dorsal vertebra on right; chronaxia normal	Motor unit discharges recorded from triceps and extensors of forearm on both sides; in addition, from biceps and hypothenar groups on left. Level, C6-C8 on right, and C5-D1 on left	Mediastinal tumor, with destruction of bodies of 7th cervical and 1st dorsal and lamina of 1st dorsal vertebra on right, verified by roentgenogram

Clinical, Laboratory and Electromyographic Data in Twenty-Four Cases of Lesions of the Spinal Cord—Continued

Case No.	Initials, Sex	Age, Yr.	History and Symptoms	Clinical Data	Laboratory Data	Electromyographic Changes	Diagnosis
15	R. H F	51	"Girdle" sensation around abdomen for 2 yr.; ascending weakness and numbness, starting in right foot, at present at midthoracic level, 1½ yr.; incontinence of urine 6-12 mo.	Spastic paraparesis; extremely hyperactive reflexes; clonus and Babinski sign in both legs; tenderness of 5th and 6th dorsal spinous processes; loss of position sense in both legs; loss of vibration sense below 10th dorsal segment	Spinal fluid: Complete block: protein 172 mg./100 cc. Roentgenogram negative	Motor unit discharges at level of spinous process of D6 on right and D4 on the left	Meningioma at level D3 on right
16	F. L. F	57	Hysterectomy for tumor 3 yr. before; pain in epigastrium and shoulders 1 mo.; weakness of both legs, starting day after onset of pain, 1 mo.; numbness from waist down 2 wk.	Spastic paraparesis with bilateral Babinski sign; tenderness of bodies of 5th and 6th dorsal vertebrae; pronounced hypesthesia below 4th dorsal level for all modalities; position and vibration sense absent in both legs and feet	Spinal fluid: Complete block; protein 282 mg./100 cc. Roentgenogram: Destruction of body of 6th dorsal vertebra	Motor unit discharges between D1-D7 on left and D3-D5 on right	Presumably metastatic carcinoma, destruction of body of 6th dorsal vertebra, verified by roentgenogram
17	H. B. M	50	Dragging of right leg, progressive for 4 yr.; numbness of right leg 3 yr.; poor sphincter control for several months	Spastic paraparesis; poorly defined sensory level (hypesthesia) at 3d dorsal (zone of hyperalgesia 4th to 7th dorsal segments), with sparing of saddle area	Spinal fluid: Complete block; protein 456 mg./100 cc. Roentgenogram negative; arrest of iodized poppyseed oil at 2d and 3d dorsal vertebrae	Motor unit activity at D5 and D6 on the right	Intramedullary tumor, verified by operation at level D4-D6 (lamina of 2d to 4th dorsal vertebrae)
18	R. D. M	61	Progressive numbness and weakness of right hand, arm, foot and leg 12 yr.; sphincteric disturbances 2-3 yr.; progressive numbness and weakness of left arm and hand 1½ yr.; progressive numbness, weakness and spasticity of left leg 1½ yr.	Horner's syndrome on right; spastic paraparesis with bilateral Babinski sign; biceps reflex moderately hyperactive on left and normal on right; triceps reflex absent bilaterally; fascicular twitches in many muscles, but more on right side; hypesthesia at 6th and 7th cervical level; anesthesia for all superficial modalities below 8th cervical to 1st dorsal level; vibratory sense abolished below 3d dorsal segment; position sense abolished for both legs	Spinal fluid: Complete block; protein 256 mg./100 cc. Roentgenogram: Osteoarthritis of lower cervical part of spine, Chronaxia normal except for slight increase in the extensors of right forearm	Motor unit discharges recorded from muscles supplied by C4-C8 on right and C1-C8 on left	Neurofibroma attached to roots of 6th and 7th cervical nerves on right
19	A. S. M	39	Lethargy and disinterestedness 18 mo.; numbness and tingling of fingers of right hand 10 mo.; progressive weakness and atrophy of right arm 3 mo.	Weakness and atrophy of all muscles of right arm and of triceps muscle of left arm; fascicular twitches of all muscles of right arm; biceps reflex greatly diminished on right; bilateral Hoffmann sign; moderately hyperactive reflexes in both legs, with suggestive Babinski sign on right; sensory status normal	Spinal fluid: No block; protein 69 mg./100 cc. Roentgenogram: Metastatic carcinoma of lower three cervical vertebrae, with moderate narrowing of spinal canal opposite 5th and 6th cervical verterbrae; osteoblastic reaction	Motor unit discharges recorded from muscles supplied by C1-C8 on right and C4-C8 on left; maximal activity recorded from right biceps (C5-C7)	Metastatic, osteoblastic carcinoma of bodies of 5th to 7th cervical vertebrae, verified by roentgenogram

Clinical, Laboratory and Electromyographic Data in Twenty-Four Cases of Lesions of the Spinal Cord—Continued

Clinical, Laboratory and Electromyographic Data in Twenty-Four Cases of Lesions of the Spinal Cord—Continued

20	J. R. M	49	Pain in back and occasional tingling of fingers 3-4 yr.; numbness of 4th and 5th fingers of right hand 5 mo.; "girdle" paresthesia and numbness of all fingers 3 mo.; weakness of arms and legs 1 mo.; sphincteric disturbance of bowel and bladder 2 wk.	Bilateral atrophy of triceps and muscles of forearm and hand; weakness of grip and of flexor muscles of forearm bilaterally; no fasciculations seen clinically; normal triceps reflexes; all other reflexes in arms absent or diminished, especially on left; absence of abdominal reflexes and hyperactivity of reflexes of both legs, with bilateral ankle clonus and Babinski sign on left; hypesthesia for pain and touch sense below 4th to 5th cervical segment; vibration sense absent and position sense decreased in both arms and legs	Spinal fluid: Complete block; protein 744 mg./100 cc. Roentgenographic evidence negative	Motor unit discharges recorded from muscles supplied by C5-C8 on left and C6-C8 on right	Intramedullary tumor seen between segments C8-C7, greatest enlargement at C5, verified by operation
21	E. F. M	33	Generalized weakness 5-6 mo.; clumsiness, tingling and numbness in both hands, particularly on right, 5-6 mo.; constipation 2-3 mo.; numbness in both legs and feet 2 mo.; difficulty in walking 3 wk.; urinary difficulties 2 wk.	Progressive tetraparesis, with spasticity of both legs and right arm; deep reflexes extremely hyperactive on right and hyperactive on left; bilateral Babinski, Chaddock and Hoffmann signs; Oppenheim sign on right; unequivocal sensory level at 5th cervical segment	Spinal fluid: Complete block (2 punctures); protein 140 and 62 mg./100 cc. Roentgenogram negative. Myelogram with iodized poppyseed oil: Level at upper border of 5th cervical vertebra. Chronaxia increased bilaterally for triceps and extensor digitorum communis muscles	Motor unit discharges recorded from muscles supplied by C5-C6 on right and C7-C8 on left; some also from trapezius bilaterally, C1-C8	Meningioma, intradural and extradural, at 4th to 5th cervical vertebrae, verified by operation
22	W. T. M	38	Injury to back 9 mo. prior to test; pain in lower part of back, pain and weakness in right leg and loss of sexual power since injury; weakness of right arm 6 mo.; numbness on medial border of right arm 4 mo.; sphincteric disturbances 3 mo.	Restriction of movements of neck; pain in middle part of neck on coughing and sneezing; weakness and hypotonia of right biceps; weakness of extensor and flexor muscles of right forearm and of grip of right hand; deep reflexes of right arm and forearm more active than those of left; clonus of flexors of forearm; bilateral Hoffmann sign, more evident on right; extremely hyperactive reflexes, with Babinski sign in right leg; hyperactive reflexes in left leg; sensory loss at 6th cervical level in right forearm, at 6th dorsal level in midchest and at 10th dorsal level on left side of chest; vibration sense impaired below 10th dorsal segment	Spinal fluid: Pressure reading not obtained; protein 66 mg./100 cc. Roentgenogram: Normal cervical part of spine; slight narrowing of intervertebral disk between 2d and 3d lumbar vertebrae	Motor unit discharges recorded from muscles supplied by C6-C8; some also from trapezius and deltoid	Small herniated disk between 5th and 6th cervical vertebrae, verified by operation
23	R. V. F	67	Cough 2 yr.; pulmonary tumor, lower lobe of right lung, diagnosed by roentgenogram 1 yr. prior to test; numbness of left leg and urinary difficulty; progressive paraplegia and beltlike sensation in lower part of chest, with numbness below, 10 days	Spastic paraplegia; sensory level at 5th and 6th dorsal segments for all modalities except vibration sense	Spinal fluid: Complete block; protein 342 mg./100 cc. Roentgenogram: Tumor of right lower pulmonary field; compression of 5th dorsal vertebra	Motor unit discharges at D4 and D5 on the left and at D7 on right	Compression of 5th dorsal vertebra, metastatic carcinoma, verified by roentgenogram
24	M. M. F	44	Radical mastectomy 5 yr. prior to test; pain between shoulder blades 2 yr.	Kyphosis in middorsal area; tenderness of 4th, 5th and 6th dorsal vertebrae; right scapula winged; otherwise normal	No spinal puncture. Roentgenogram: Marked collapse of 6th dorsal vertebral body; anterior margin of body of 5th dorsal vertebra indistinct; narrowing of body of 8th dorsal vertebra in vertical direction, with indistinct anterior margin	Motor unit discharges at D5-D7 on right and D6 on left	Metastatic carcinoma, involving 5th, 6th and 8th dorsal vertebrae; collapse of 6th dorsal vertebra, verified by roentgenogram

brae, adhesive arachnoiditis with cyst formation, syringomyelia with cyst and myelomalacia were each present in 1 case.

In 17 cases the localization of the lesion by means of spontaneous motor unit discharges was considered satisfactory. In 4 of these (cases 4, 8, 12 and 24) both the upper and the lower level of the lesions were determined precisely; in 10 other cases (1, 2, 14, 15, 17, 18, 19, 20, 21 and 22) the electromyographic level extended for one segment above or below that of the structural lesion. A relatively small amount of activity was also recorded for a short time from the trapezius muscle in case 21 and from the trapezius and deltoid muscles in case 22. In the other 3 cases (3, 10 and 11) the upper levels were correctly determined, while electromyographic changes were recorded in several segments below the verified levels of the lesions. In 1 of these cases the lesion was a metastatic carcinoma; in 1, the second case, it was an intramedullary glioma (spongioblastoma), in which the lesion might actually have extended below the area exposed at operation, and in the third case adhesive arachnoiditis was present.

In case 6, in which the fifth dorsal vertebra was fractured, the upper level of motor unit activity was found at the eighth dorsal segment, one segment below the one (seventh dorsal) presumably injured by the fracture.

In 4 other cases (5, 13, 16 and 23) spontaneous motor unit activity was recorded about equally over a wide range of segments of the cord, including the proper level of the lesions in each instance. For practical purposes of localization, the lesion in these cases was not considered sufficiently well localized. However, in 2 cases the lesion was metastatic carcinoma, and in 1, Paget's disease, both processes being anatomically less well limited than is fibroma, for example. Finally, false levels were obtained in 2 cases (7 and 9), both instances of meningioma.

Fascicular twitches were observed clinically in only 6 cases, in 5 of which the lesion was cervical. In 4 of these cases the fasciculations occurred at the level of the lesion, and in 1 case they were noted several segments above that of the lesion. In the case of Paget's disease fasciculations were recorded from both gastrocnemius muscles, again, in a distribution several segments removed from the established site of the lesion (see comment in the preceding paragraph).

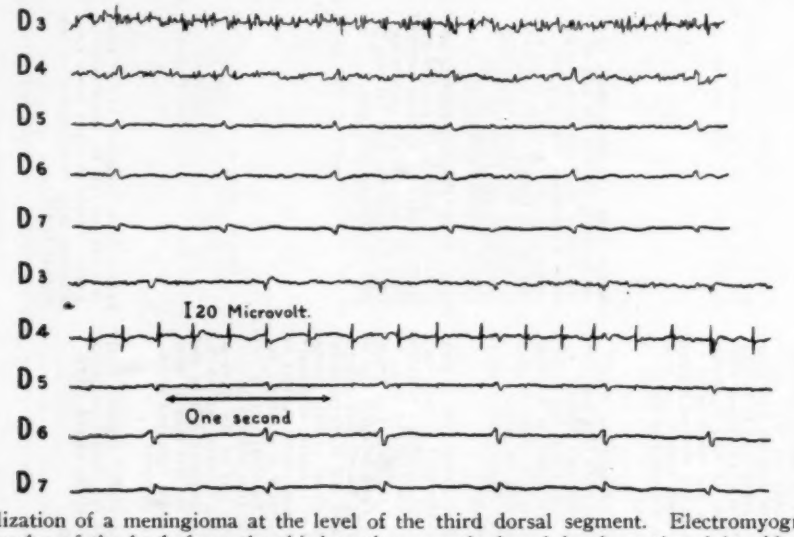

Fig. 1.—Localization of a meningioma at the level of the third dorsal segment. Electromyograms were taken from the long muscles of the back from the third to the seventh dorsal level on the right side (upper records) and on the left side (lower records). For details, see description in the text.

Clinical motor signs of localizing value were present in 13 cases. In 11 of these cases the lesion was cervical; in 1, dorsolumbar, and in 1, lumbosacral. Questionable motor signs were noted in 2 cases of a cervicodorsal lesion and in 1 case of a lumbosacral lesion. In 6 cases of a dorsal lesion paraparesis or paraplegia was observed, but this was of no localizing value. In 2 cases of a dorsal lesion no motor signs were noted.

Clinical sensory levels were found to be of correct localizing value in 12 cases—6 of a cervical lesion, 2 of a cervicodorsal lesion, 3 of a dorsal lesion and 1 of a dorsolumbar lesion. Vague and doubtful sensory levels were noted in 5 cases—2 of a cervical, 2 of a dorsal and 1 of a lumbosacral lesion. No sensory levels were observed in 6 cases—2 of a cervical, 1 of a

cervicodorsal, 2 of a dorsal and 1 of a lumbosacral lesion. In 1 case, of a dorsal lesion, a false sensory level was obtained.

Roentgenographic studies alone were used to establish the diagnosis in 7 cases. In another case the correct diagnosis was made on the basis of roentgenographic evidence and verified by operation. In 6 cases the correct level was

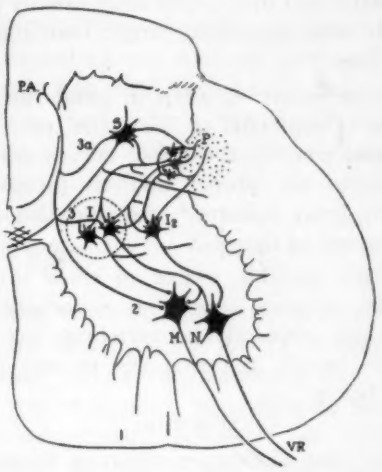

Fig. 2.—Semidiagrammatic drawing of a segment of the spinal cord of a cat (from Lloyd,[9] page 542). *E* indicates small cells of the external basilar region; *I*, intermediate gray nucleus of Cajal; I_2, other neurons of the intermediate region; *M.N.*, motoneurons; *P*, pyramidal tract and fibers; *P.A.*, primary afferent collaterals; *S*, solitary cells of the dorsal horn; *V R*, ventral root, and *2*, *3* and *3 a*, terminal collaterals of the primary afferent system.

This diagram illustrates the possible routes by which "distant" stimuli may reach the motoneuron (anterior horn cell with its axon).

established by myelograms obtained with iodized poppyseed oil or air. In 7 cases the roentgenograms showed an apparently normal condition, or the evidence was insignificant. False levels were obtained in 4 cases, in 1 of which the diagnosis was corrected by a subsequent myelogram.

In figure 1 an actual record is presented. The lesion (case 15) was a meningioma at the level of the third dorsal segment on the right side. The long muscles of the back were explored on each side at the levels of the spinous processes from the third to the seventh dorsal segment. The figure consists of two strips, the upper from the right side and the lower from the left side. Time and calibration for both are designated on the lower record. In the upper record (right side) discharges of several motor units are recorded at D_3 and some at D_4. In the lower record (left side) a single motor unit is seen at D_4 discharging at the rate of about 4 per second. At D_5 suggestive discharges of another distant single motor unit can be seen. In the other leads an artefact produced by the electrocardiogram is the only activity recorded.

COMMENT

Elsberg [1] noted fascicular twitches in cases of both intramedullary and extramedullary tumors of the cord; he reported that they were present in wasted muscles, as well as in muscles showing no evidence of atrophy. Rosett [5] reported that muscular twitches at the level of lesions of the cord can be elicited by hyperventilation. The

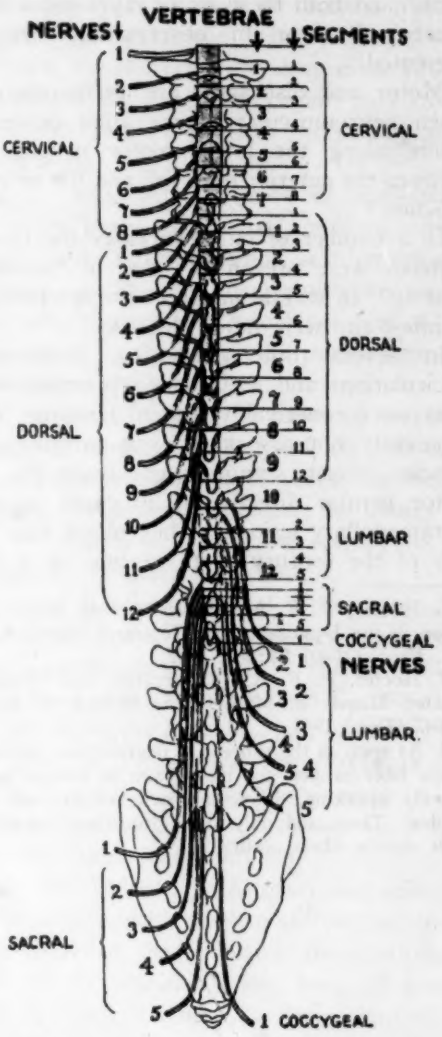

Fig. 3.—Diagram from Elsberg,[1] showing the relation of the segments of the cord to the vertebrae.

latter method, in our opinion, is nonspecific, as tetany produced by overbreathing is usually generalized, rather than focal.

5. Rosett, J.: The Experimental Production of Rigidity, of Abnormal Involuntary Movements and of Abnormal States of Consciousness in Man, Brain **47**: 293, 1924.

In our own observations, motor unit action potentials, rather than grossly visible fasciculations, were used for the purpose of localization. The motor unit action potentials constitute the physiologic equivalent of the contraction of a group of muscle fibers supplied by a single axon.

In order properly to evaluate the significance of motor unit action potentials, one must keep in mind the fact that all forms of innervation of striated muscle are managed by activation of motor units. This is seen in movement,[6] as well as in the muscular tenseness of unrelaxed subjects,[7] and both these states represent a definite source of error in observations like those presented.

Motor unit discharges are, furthermore, seen when neuromuscular degeneration occurs anywhere along the lower motor neuron, i. e., between the anterior horn cell and the neuromyal junction.[8]

In a number of our own cases the fascicular twitches were presumably due to "subclinical" wasting. In several instances the atrophies were manifest and were noted clinically.

In several other instances, however, the fasciculations and their action potential equivalents were conceivably due to irritative stimuli apparently not associated with atrophy of the muscles. Such stimuli might reach the lower motor neuron directly, as in cases of certain extramedullary lesions. They might also act by way of the sensory roots, setting up a reflex. Finally, stimuli arising in intramedullary structures some distance away from both sensory and motor roots might act by reaching the internuncial neuron.

Figure 2 (Lloyd[9]) is a semidiagrammatic drawing of a segment of the cord in which the relation of the "interneuron" to other segmental structures of the cord is indicated. A mechanism of this nature is perhaps responsible for the fact that motor unit discharges were usually recorded from an area somewhat larger than that of the actual lesion.

It is necessary to keep in mind the variable relation of segments of the spinal cord and the vertebrae, whereas the spinal nerves always correspond to the proper spinous processes. A diagram from Elsberg,[1] showing this relation, is presented in figure 3.

Another possible source of error is the fact that the spinous processes, especially of the middle and lower dorsal vertebrae, are of considerable length, covering one to two vertebral bodies below.

SUMMARY

Motor unit discharges recorded from relaxed muscles may indicate the level of a lesion of the spinal cord, even in the absence of clinical manifestations suggestive of involvement of the region of the anterior horn cells or the motor roots.

In 17 of 24 cases the structural lesion was satisfactorily localized with the method briefly described. In 1 additional case the localization by electromyography indicated a level one segment below the clinical level. In 4 cases motor unit discharges were obtainable over too many segments of the cord for precise localization. False localizations were made in 2 cases.

710 West One Hundred and Sixty-Eighth Street.

6. Hoefer, P. F. A.: Physiology of Motor Innervation in the Dyskinesias, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:502, 1942.

7. Hoefer, P. F. A.: Innervation and "Tonus" of Striated Muscle in Man, Arch. Neurol. & Psychiat. **46**:947 (Dec.) 1941.

8. As soon as the process of degeneration attacks the muscle fiber proper, the motor unit is broken up, and, properly speaking, fascicular twitches are no longer possible. Then, and only then, "fibrillary" twitches of single muscle fibers occur.[2]

9. Lloyd, D. P. C.: The Spinal Mechanisms of the Pyramidal System in Cats, J. Neurophysiol. **4**:525, 1941.

INCIDENCE OF METASTASES TO THE NERVOUS SYSTEM

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While benign neoplasms of the nervous system are frequently encountered, malignant metastases to neural tissues are not numerous. In the literature one finds records of metastases to the nervous system from various organs; yet no one has so far undertaken the arduous task of collating the incidence of all recorded cases of carcinoma and sarcoma metastasizing to the nervous system with the primary lesion in other parts of the body.

According to most observers, cancer of the breast is the most frequent source of metastases to the brain. However, following that, in the order of their frequency, according to Redlich,[1] are the rare cylindric epithelial cell carcinoma of the bronchial mucosa and carcinoma of the gastrointestinal tract, the esophagus and the mediastinum. In Krastnig's material, cited by Levin,[2] the primary sites of neoplasm in 39 cases of cancer of the brain encountered in a series of 817 brains were as follows: the prostate, in 22.2 per cent; the breast, in 18.8 per cent, and the uterus, in 3.4 per cent. In 227 cases of cancer of the stomach he did not find a single metastasis to the brain, and that is true for my material.

In the literature I find only six compilations of the reported cases of cerebral metastases from various organs. Grant [3] stated that a study of the statistical tables based on his series of 49 cases of metastatic malignant growth in the brain showed that carcinoma was almost twice as frequent as sarcoma and that in almost one half of the cases of metastatic carcinoma the primary focus was in the breast. Of 36 cases of intracranial carcinoma, the primary focus, when verified, was in the breast in 6 cases, in the lungs in 6 cases, in the mouth and sinuses in 2 cases, in the generative organs in 1 case and in the liver and intestine in 1 case; in 4 cases the primary focus was unknown. Of 13 cases of sarcoma metastasizing to the brain, the primary focus was verified in 6, the site being the skin or the retina in 3 cases and the generative organs in 1 case; in 2 of these cases the primary neoplasm was a hypernephroma.

Brunner [4] reported 73 cases of metastatic tumor of the brain, the primary seat of which was in the lungs in 28 cases and in other organs in 23 cases; in 12 cases the primary neoplasm was a hypernephroma. In 4 to 5 per cent of his cases of cancer of the breast the primary tumor metastasized to the brain.

Pass [5] reported that of 32 cases of cerebral metastatic carcinoma, the site of the primary tumor was the bronchus in 16 cases, the breast in 10 cases, the prostate in 1 case, the kidney in 1 case, the uterus in 1 case, the epipharynx in 1 case and the stomach in 2 cases.

According to Behrend and Schiff,[6] of 200 tumors of the brain, 20, or 10 per cent, were metastatic carcinomas. Of these, the site of the primary focus was the adrenal in 2 cases, the breast in 4 cases, the bronchus in 2 cases, the ala of the nose in 1 case and the cervix of the uterus in 1 case; in 3 cases the primary lesion was a hypernephroma, and in 6 cases the site of the primary focus was unknown.

Globus and Meltzer,[7] in 33 cases of carcinoma of the brain in which complete autopsy was performed, observed the following distribution of the sites of the primary lesion: lung, 19 cases; thyroid, 4 cases; rectum, 3 cases; sigmoid, 2

From the Neuropsychiatric service of the New York Cancer Institute, Welfare Island, N. Y.

1. Redlich, E.: Hirntumor, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1912, vol. 3, p. 559.

2. Levin, I.: Metastases of Cancer in the Central Nervous System, J. Nerv. & Ment. Dis. **45**:481, 1917.

3. Grant, F. C.: Concerning Intracranial Malignant Metastases: Their Frequency and the Value of Surgery in Their Treatment, Ann. Surg. **84**:642, 1926.

4. Brunner, W.: Ueber die Häufigkeit von Gehirnmetastasen bösartiger Geschwülste, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:793, 1936.

5. Pass, E. K.: Zur Klinik der cerebralen Carcinomametastasen, Nervenarzt **11**:385, 1938.

6. Behrend, C. M., and Schiff, E.: Ueber Hirnmetastasen, Nervenarzt **11**:57, 1938.

7. Globus, J. H., and Meltzer, T.: Metastatic Tumors of the Brain, Arch. Neurol. & Psychiat. **48**: 214, 1942.

cases; stomach, 1 case; adrenal glands, 1 case; kidney, 1 case, and prostate, 1 case; the origin of the metastasis was unknown in 1 case.

In addition, there were 3 cases in which a complete autopsy was not done but an operative procedure indicated clearly the seat of the primary lesion: In 1 case the primary focus was a carcinoma of the breast; in another, a pigmented mole on the left leg, and in the third, a small melanotic tumor in the skin of the right foot.

Fried [8] reported that metastases to the brain occurred in 16 of his series of 47 cases of carcinoma of the lung.

In 1923 the first cancer institute was established in the Department of City Hospitals of New York for the exclusive purpose of treating malignant growths of all forms. An opportunity was then offered for a study of the frequency of metastases to the nervous system. It is obvious that an accurate diagnosis must be based on autopsy. Since, however, it is necessary to secure permission for autopsy and, unfortunately, such permission is rare, one must allow for errors. In every case, however, in which a primary malignant growth was indicated, the diagnosis was verified by autopsy or necropsy.

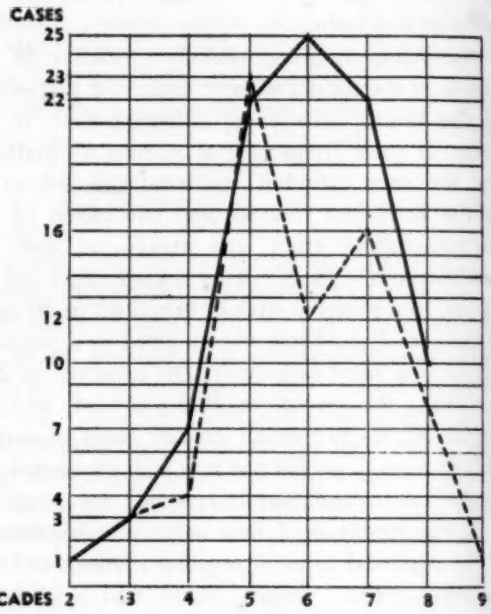
I have examined the records for admissions over a period of eight years, from 1935 to 1942 inclusive, representing 6,761 cases. Metastatic carcinoma of the nervous system was present in 143 cases, in some of which the diagnosis was verified by autopsy, with an incidence of approximately 2.15 per cent.

In the material from this institute, cancer of the breast had the highest frequency of metastases to the brain; of such metastases there were 14 cases. This incidence coincides with that of other observers. Next in the order of frequency with which they metastasized to the brain were carcinoma of the lung, 8 cases; carcinoma of the pharynx and larynx, 8 cases each; carcinoma of the tongue, 4 cases; carcinoma of the uterus, 3 cases; carcinoma of the rectum and skin, 2 cases each, and carcinoma of the bladder, hard palate and antrum, 1 case each. As the primary focus of metastasis to the mastoid bone, with involvement of the facial nerve and consequent typical peripheral paralysis and loss of taste in the anterior two thirds of the tongue, cancer of the breast contributed 4 cases; cancer of the auditory canal, 3 cases, and cancer of the tongue and tonsil, 1 case each.

To metastases of the nerve plexuses, cancer of the lung, skin, rectum and kidney contributed 2 cases each, and cancer of the breast, larynx, skeletal bones and tongue, 1 case each. To involvement of the cervical sympathetic ganglion, with a resultant Horner syndrome, cancer of the breast contributed 4 cases, and cancer of the tonsil, 1 case.

METASTASES INVOLVING THE SPINAL CORD

The order of frequency with which metastases involved the spinal cord was practically on a par with that for the brain. Cancer of the breast, with 18 cases, and cancer of the prostate, with 15 cases, had the highest frequency; then came cancer of the sigmoid and colon, with 4 cases each; cancer of the spine, stomach, ileum and kidney, with 3 cases each; cancer of the pharynx, bladder, rectum and uterus, with 2 cases each, and cancer of the skeletal bones, mandible, testicles and ovary, with 1 case each. The symptoms of course depended on the site of the lesions in the nervous system. It is significant that in all but 1 case of cancer of the prostate the central portion of the cord was involved in the form of syringomyelia.



In age incidence and number of cases the males show a slight predominance. Values for males are indicated by a solid line; values for females, by a broken line.

8. Fried, B. M.: Primary Carcinoma of the Lung, Baltimore, Williams & Wilkins Company, 1932, p. 125.

SARCOMA

During the period under study only 10 cases of sarcoma metastasizing to the nervous system were encountered, an incidence of approximately 0.15 per cent. The distribution was as follows: Sarcoma of the thigh metastasized to the lumbosacral plexus in 1 case and to the spinal cord in another; in 3 cases of involvement of the cord the site of the primary sarcoma was the spine, and in 2 cases it was the ileum, in 1 case the skeleton and in 1 case the jaw; in 1 case a sarcoma of the heel metastasized to the brain.

The age incidence for males was slightly higher than that for females (chart), and slightly more males than females were affected. For males the peak of the incidence fell in the sixth decade, while for females it came in the fifth decade. From these points the frequency for both sexes declined, the occurrence of cerebral metastases stopping abruptly in the eighth decade in males and continuing into the ninth decade in females.

Miss Lopez, statistician to the New York Cancer Institute, cooperated in this work.

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TORULAR GRANULOMA SIMULATING CEREBRAL TUMOR

REPORT OF TWO CASES

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It is not generally recognized that torulosis of the brain may simulate an intracranial tumor. In the literature on torular infections, meningitis is emphasized as the common lesion, with disregard of the importance of gross granulomas. Probably a large granuloma simulating a true neoplasm occurs more frequently than the number of reported cases would indicate. The paucity of recorded cases may be explained by the difficulty of diagnosis, especially when studies of the spinal fluid reveal nothing significant. The comparative rarity of this entity seems to warrant a report of the following 2 cases.

REPORT OF CASES

CASE 1.—*History.*—A white woman aged 49 was admitted to the hospital on Nov. 18, 1941, in a critical state. She was confused, irrational and stuporous, and the history obtained from the family did not appear to be reliable. She apparently had had periodic headaches associated with nausea and vomiting for at least one year. In August 1941 operation had been performed elsewhere for what was thought to be a fibroma of the uterus, but microscopic studies were not made. Pellagra developed thereafter, as the result of persistent vomiting. The headaches had steadily increased in intensity and were followed by diplopia, impairment of vision and unsteadiness of gait. Changes in personality, the nature of which were vague and indefinite, had been present for several weeks.

Examination.—On admission to the hospital the patient presented a picture of extreme emaciation, with mental confusion, disorientation and hallucinations. The skin of the arms, hands and neck and the mucous membranes of the oral cavity and tongue showed the typical lesions of advanced pellagra. The heart and lungs were normal, and the blood pressure was 155 systolic and 88 diastolic. The outstanding neurologic signs were rigidity of the neck and a suggestive Kernig sign. The eyegrounds were normal. There were palsy of the sixth nerve, bilaterally, with horizontal nystagmus on her looking to the right, and hypesthesia of the right side of the face. The cranial nerves were otherwise normal. The deep reflexes were hypoactive, and the abdominal and plantar reflexes were normal. The mental condition varied from semistupor to periods of euphoria with facetiousness. Roentgenographic examination of the skull and chest revealed nothing abnormal.

Course.—While the patient appeared to be ill, her condition did not seem to warrant an emergency measure. However, before further studies could be made, respiratory failure suddenly developed, and she died. Permission for autopsy was limited to examination of the brain.

Autopsy.—The calvarium was normal, and the dura stripped with ease in all areas. There was a mild excess of subdural fluid, which was clear, but no gross lesions were apparent in the dura. Superficially, the brain showed two distinct tumor masses, one in the right cerebellar hemisphere and the other in the left occipital lobe. The former, measuring 4 by 5 cm., apparently involved the major portion of the cerebellar hemisphere, while the latter superficially measured less than 1 cm. in diameter. No superficial lesions were apparent elsewhere. The gyri were moderately flattened and widened and the sulci shallower than normal. The arachnoid generally had its normal thin, glistening appearance, but over the lesion in the left occipital lobe it showed granular thickening and adherence. The arachnoid over the cisterns was not unusually thickened or adherent. There was an obvious pressure cone over the cerebellar tonsils.

Cut section revealed that the cerebellar tumor had involved three fourths of the hemisphere and measured 3 by 4 by 4 cm. (fig. 1). It had sharply compressed the hemisphere, but in the lateral and anterior portions it extended well to the surface. The tumor showed a striking tendency to separate easily from the surrounding tissue, with little or no evidence of active invasion or reaction other than pressure necrosis. The tumor was made up of a multitude of small loculated cystic cavities filled with thick mucoid material which did not flow; these cavities were separated by thin strands of loose, friable connective tissue. The cysts, unlike the usual cystic cavities, remained open and did not collapse on being cut across. The capsule of the tumor was thin, measuring less than 2.3 mm., and was rather firm.

The lesion in the left occipital lobe reached the periphery along the mesial surface and when fully exposed measured less than 2 by 1.5 cm. It was similar in all respects to the cerebellar granuloma and, like it, appeared to be sharply circumscribed and easily separated from the surrounding tissue.

Serial sections of the brain revealed another small granuloma, measuring less than 2 by 2 cm., in the right occipital lobe (fig. 2), immediately adjacent to the calcarine fissure. There was no other gross lesion in any area of the brain and no frank evidence of leptomeningitis.

Microscopic Study (Dr. Warren Matthews).—Numerous sections from the three lesions showed similar features. Each lesion was sharply separated from the brain tissue by a thick capsule of lamellated fibrous tissue (fig. 3). There was little, or no, reaction of the brain tissue to the lesion. Small blood vessels in the adjacent portion of the brain were sometimes sur-

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rounded by round inflammatory cells. Careful study showed occasionally a torula lying near a small blood vessel just outside the capsule of the lesion; as a whole, however, the capsule seemed to have efficiently walled off the organisms. In the fibrous tissue forming the capsule were many leukocytes; few of these were polymorphonuclear in type; most of them were phagocytes, lymphocytes and plasma cells. Giant cells were not seen. Many of the phagocytes had vacuolated cytoplasm, and this was true of many of the connective tissue cells. Occasionally an attempt at phagocytosis of a torula was noted. However, this was not common and must have been ineffective.

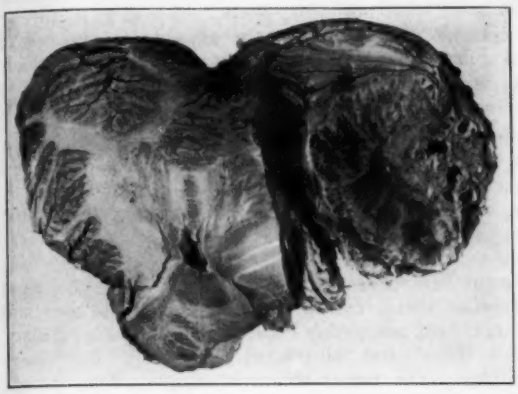

Fig. 1 (case 1).—Gross picture of granuloma of the right cerebellar hemisphere.

The central, and larger, portion of each lesion consisted almost wholly of solid masses of torulas, embedded in a thin network of connective tissue (fig. 4). Where the organisms were most numerous, leukocytes were scarce. With the dehydration used in preparation of the slides, the organisms appeared to have lost considerable fluid, since they lay within clear spaces, from the surface of which they had shrunken. They appeared as round or oval, light blue or lavender bodies when stained with hematoxylin and eosin. They consisted of rather glassy, homogeneous and agranular material. Each organism appeared isolated, and budding was seldom encountered.

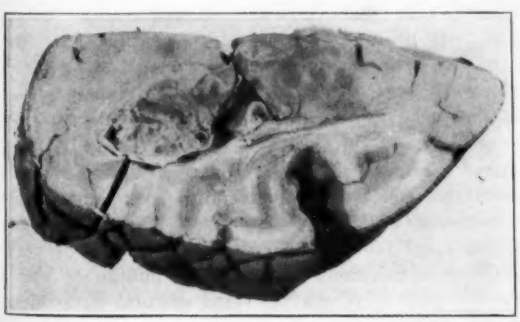

Fig. 2 (case 1).—Gross picture of granuloma of the right occipital lobe.

The patient was admitted to the hospital obviously in the terminal stage of a progressive disease suggestive of an expanding intracranial lesion. She died before either complete study or operation could be carried out. Autopsy showed three distinct, large, isolated tumor masses in the brain, which grossly suggested metastatic colloid

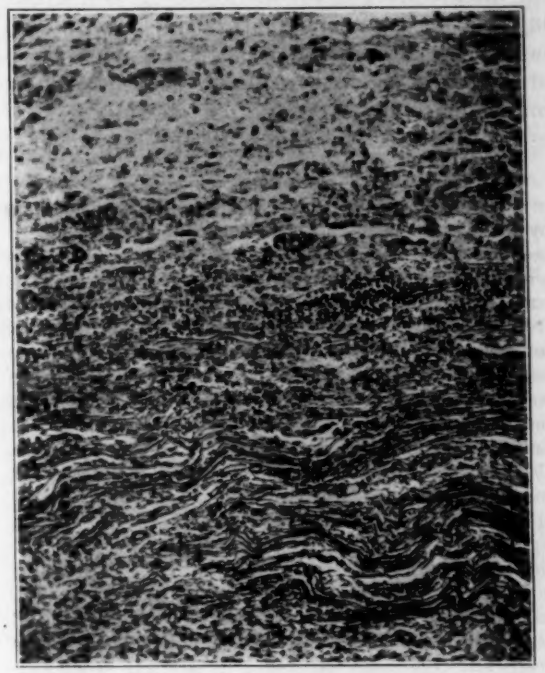

Fig. 3 (case 1).—Low magnification of the cerebellar lesion, showing peripheral portion of the granuloma.

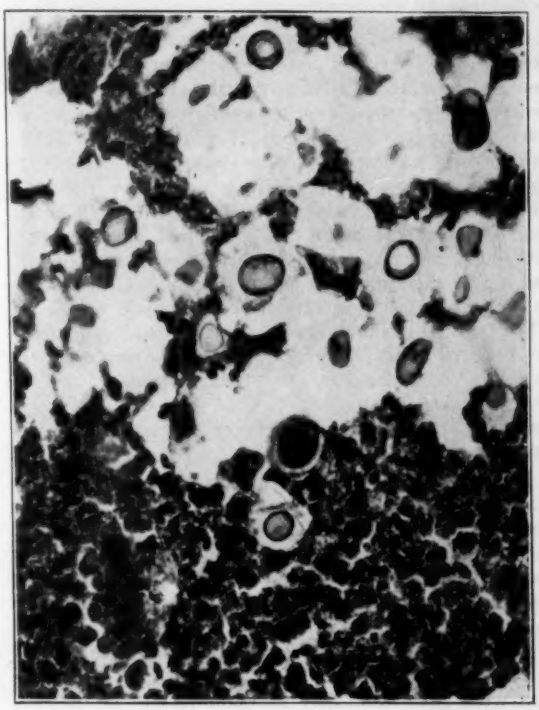

Fig. 4 (case 1).—High magnification of the cerebellar lesion, showing torulas within the granuloma.

carcinoma. It was not until the microscopic studies were completed that the true nature of the disease process was disclosed. It is interesting that the roentgenograms of the chest showed no primary pulmonary lesions and that the brain at autopsy revealed no evidence, either grossly or microscopically, of generalized meningitis, such as is usually seen in cases of torulosis.

CASE 2.—*History.*—A white man aged 36 was seen in April 1943. In December 1941 he had been rejected by the Army because of a lesion in the chest. He had been admitted to the State Tuberculosis Sanatorium with a presumptive diagnosis of pulmonary tuberculosis, but four months later Torula histolytica was cultured from the sputum and gastric contents. After treatment for several weeks with potassium iodide and a vaccine made of his own cultures, the size of the pulmonary lesion regressed. He stated that while he was in the sanatorium a lumbar puncture was made and the fluid was found to be normal in all respects. In June 1942, because of pain in the neck and headaches, he entered Duke University Hospital. Here again, studies of the spinal fluid were reported to reveal nothing significant. The headaches and pain in the neck recurred intermittently, but in March 1943 they began to be more severe and were associated with nausea and vomiting. He also began to have severe dizziness, associated with staggering gait. The dizziness was practically continuous, consisting of whirling sensations, and was aggravated by turning of the head. There was no associated tinnitus and no difficulty in hearing. Blurring of vision gradually developed, as well as occasional double vision on his looking to the right.

Examination.—The patient was well developed. He complained bitterly of headache. General examination revealed generalized adenopathy, the glands being small, tender and movable, and suppression of breath sounds over the upper lobe of the right lung, without rales or evidence of cavitation. There was slight rigidity of the neck but no definite Kernig sign. The left optic disk showed low grade papilledema with small recent hemorrhages; the right disk presented only marginal blurring. There were coarse nystagmus on the patient's looking to the right and fine nystagmus on his looking to the left. The right lateral rectus muscle was weak. The rest of the cranial nerves were normal. There was no localized motor weakness or dysmetria in any of the extremities, but the gait was slightly ataxic. The deep reflexes were brisk and equal on the two sides, and there were no pathologic reflexes. Sensory examination showed no abnormalities.

Roentgenograms of the skull revealed nothing abnormal, and recent roentgenograms of the chest showed fibrosis in the right infraclavicular region. The spinal fluid pressure was 350 mm. of water; examination of the fluid showed a cell count of only 6 cells per cubic millimeter; the protein measured 184 mg. and the sugar 89 mg. per hundred cubic centimeters, and cultures made in three laboratories were negative for the torula. Repeated studies of the spinal fluid during the next week gave essentially the same results, all cultures being sterile, and at no time was the cell count remarkable. On April 20 air studies of the ventricles were carried out, with the use of local anesthesia. Parafrontal trephine openings were made, and the cortex was observed to be under excessive pressure. The arachnoid was unusually thick and tough on both sides, and there was an excess of subdural and subarachnoid fluid. Both anterior horns were encountered at their normal depth and in the normal position, and it was apparent that hydrocephalus existed. The roentgenograms revealed symmetric dilatation of the lateral and third ventricles, and air was seen to extend below as far as the lower third of the aqueduct, which was also dilated. The changes were those of an obstructing lesion of the posterior fossa. Although a torular granuloma was suspected, the absence of changes in the spinal fluid, together with evidence of an obstructing lesion of the fourth ventricle, seemed to justify exploration.

Operation.—Suboccipital craniotomy was carried out on the right side. Both cerebellar hemispheres were under tension. As the dura was opened, thickening of the arachnoid, with adherence to the hemispheres and dirty gray discoloration, was observed. As the arachnoid over the cisterna magna was opened, a tumor was brought into view. This lesion arose in the right cerebellar tonsil, extended mesially and expanded into a large, firm, completely encapsulated and isolated mass, which filled and obstructed completely the fourth ventricle. The tumor measured roughly 3 by 3 cm.; it was relatively avascular and reddish gray and could not be separated sharply from the lower pole of the cerebellar hemisphere. There were no lesions over the surface of either hemisphere suggestive of either meningitis or cystic degeneration, such as one usually sees in cases of torular infection. Even though we were cognizant of the possibility that this lesion was a torular granuloma, the tumor seemed grossly to resemble an ependymal growth. Generous removal of the mass was then carried out, until a free flow of the ventricular fluid was established through the fourth ventricle, and then, with the idea in mind of giving the patient high voltage roentgen therapy, the wound was closed. The patient stood the operative procedure well and was relieved of his symptoms.

Histologic Examination.—Microscopically, sections of the tissue removed showed no normal brain structure. The tissue consisted of granulomatous and glial tissue, within which was a large number of scattered spherical structures. The latter were several times larger than ordinary cells and contained dark, centrally placed nuclei with no differentiation of chromatin. The cytoplasm was clean and unstained. Although no spores or buds were present, these cells were typical torulas. For the most part the tissue was solid, with no areas of cystic or mucoid degeneration.

After operation the patient did well and was fairly comfortable and afebrile by the fifth postoperative day. Examination of the spinal fluid on the seventh day showed a cell count of 7 (6 monocytes and 1 polymorphonuclear leukocyte) per cubic millimeter and a protein content of 67 mg. per hundred cubic centimeters. He was discharged on the twelfth day, without symptoms. On August 2 he returned, somewhat reluctantly, for reexamination. For two weeks he had experienced his old headaches, associated with nausea and vomiting, and had had instability in gait. The area of decompression was taut and bulging; there was definite papilledema, of 2 D., and nystagmus was present in the right eye on lateral gaze. Readmission to the hospital was necessitated by unbearable headaches. Studies of the spinal fluid on this admission showed pleocytosis for the first time, with a count of 165 cells (all mono-

cytes) per cubic millimeter, and the cultures were now positive for T. histolytica.

Second Operation.—On August 14 the trephine exposure in the right anterior region was reopened, and the right anterior horn was tapped. Fifty cubic centimeters of clear fluid was obtained and a Frazier needle

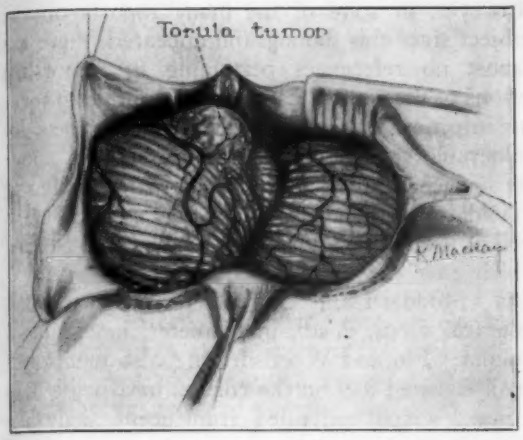

Fig. 5 (case 2).—Drawing of the granuloma in the right cerebellar hemisphere made at operation, showing the site of the lesion and its gross appearance.

left in place. On August 16 a second operation was done, the former suboccipital craniotomy opening on the right side being converted into a conventional cross bow incision and a generous decompression of the bone carried out. As the scalp was reflected over the bony defect on the right, an extracerebellar cyst, which was lined with thickened, glistening dura, was opened. Covering the surface of the superior pole of the right cerebellar hemisphere was a glistening, clean, whitish exudate, which seemed to be continued superiorly into the duplication of the dura lining the cyst. The right cerebellar hemisphere was observed to be almost twice its normal size, and the lower one-half was involved with a nodular, white, firmly adherent tumor, which displaced the mesial and lower portions of the right cerebellar hemisphere beyond the midline to the left, with complete obstruction of the lower end of the fourth ventricle (fig. 5). The mass was sharply demarcated from the cerebellar hemisphere and superficially appeared to be firm. As the tumor was dissected and rolled inferiorly from the cerebellum, a difference in its character became apparent. Whereas the outer, and exposed, portion had been firm and solid, the deeper portion was softer and was seen to be a deep yellow, being made up of a mass of innumerable, small loculated cysts which contained a mucinous-like material which did not flow on section. Approximately four fifths of the tumor was removed and the fourth ventricle completely decompressed. The portion of the tumor which remained had wrapped itself about the emerging lower cranial nerves and the upper cervical portion of the cord. More extensive examination revealed thickening of the arachnoid over the left cerebellar hemisphere, and the arachnoid had a foamy, dirty gray appearance, suggestive of a meningitic process. After operation the patient did well for three days and then lapsed into coma, with high fever and signs of pulmonary involvement. He died on the fifth postoperative day. A complete autopsy was performed.

Autopsy.—The brain weighed 1,475 Gm. The dura, except over the region of the recent craniotomy, stripped easily. In this area there was some adherence, and as the tentorium was incised, approximately 100 cc. of slightly bloody fluid gushed from the posterior fossa. The external surface of the cerebral cortex showed no evident lesions, and the arachnoid over the cortex was glistening. Inspection of the cerebellum revealed a tumor mass protruding from the right hemisphere (fig. 6). This tumor, when viewed from the inferior surface, was a nodular, yellowish gray mass, measuring grossly 4 by 5 cm. The superior portion of the mass occupied the inferior one third of the hemisphere. This surface was quite different from the inferior aspect, revealing numerous large and small loculated cystic cavities, separated by bands of dense, fibrous tissue and containing gelatinous and granular material. The lesion extended inferiorly to involve one-half the lateral and inferior portion of the hemisphere and compressed the brain stem. The capsule in some areas was 0.5 cm. in thickness. If the capsule was grasped, the cyst could easily be shelled out, a procedure which indicated the absence of invasive tendency.

Serial sections of the brain revealed no other gross lesion and no evidence of meningitis other than mild thickening of the arachnoid over the base of the brain.

Examination of the viscera showed no significant lesions except in the lungs and spleen. Cysts similar to those in the brain were present in the upper lobe of the right lung; small cysts were seen in the spleen on microscopic examination.

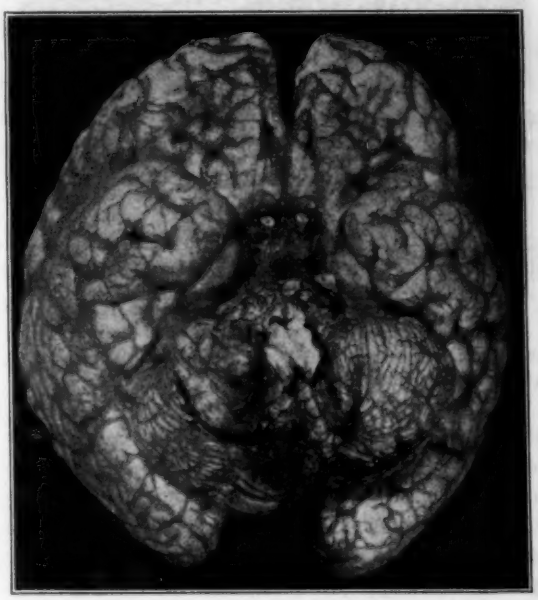

Fig. 6.—Gross specimen of the brain, showing the granuloma protruding from the inferior surface of the right cerebellar hemisphere and sharply distorting the brain stem. The absence of meningeal lesions is evident.

Microscopic Study (Dr. Warren Matthews).—The lesion was similar to the tumors in case 1; it was separated from the surrounding brain tissue by a thick capsule of fibrous tissue (fig. 7), containing many leukocytes, chiefly phagocytes, lymphocytes and plasma

cells. There were no giant cells. Outside the capsule there was no reaction of the tissue to the lesion. The central portion of the lesion consisted of masses of torulas, separated by a thin meshwork of connective tissue.

This patient, with a history of proved torular infection of the lung, presented a clinical picture of increased intracranial pressure, with localizing signs pointing to the posterior fossa. The presence of an infection of the central nervous system similar to that in the preceding case was considered, but repeated studies and cultures of the spinal fluid showing nothing of significance, this possibility seemed to be excluded. When the tumor was visualized at operation, it in no way

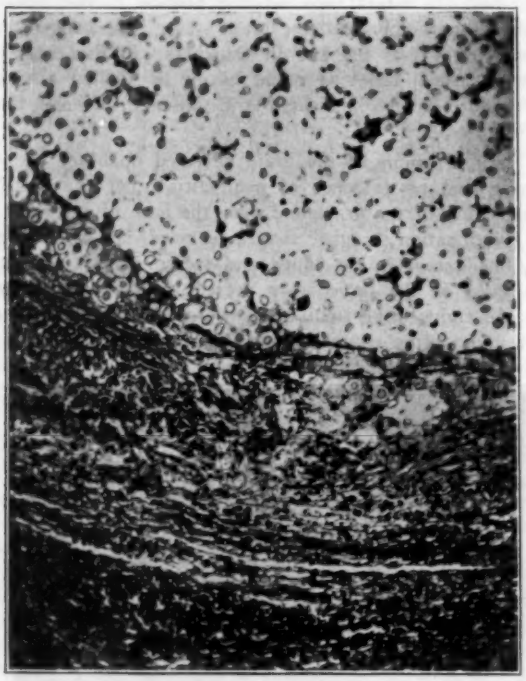

Fig. 7 (case 2).—Low magnification of the cerebellar granuloma, showing the wall and cavity of the cyst, within which can be seen torulas.

resembled torular lesions which had previously been described; rather, it grossly appeared to be an ependymal tumor and was considered to be such until microscopic studies proved its true nature. The patient did extremely well after operation for approximately two months; he then showed evidence of recurrence of increased intracranial pressure and presented meningitis on the second admission. The second operation was undertaken in the hope of relieving his acute distress by means of a more generous area of decompression; it also was thought that because the pulmonary lesion had partially healed, life might at least be prolonged through relief of the obstruction.

REVIEW OF THE LITERATURE

Prior to Stoddard and Cutler's [1] report, in 1916, of a case of torular meningitis, little was known concerning infection with this organism. In 1931 Freeman [2] published his classic study of the pathologic and other aspects of the disease. However, in spite of the many reports on the subject since this monograph appeared, there are almost no references pertaining to tumor-like lesions of the central nervous system due to torular infection. Von Hansemann [3] described innumerable small cysts protruding slightly above the surface of the brain and filled with translucent colloidal material that did not flow on section, as well as a large colloidal mass in the basal ganglia which gave the impression of an acellular myxoma. Stoddard and Cutler referred to a solid, spherical focus, 2 cm. in diameter, in the basal ganglia. Flu and Woensdright [4] also mentioned small elevated foci on the cortex, measuring 1 to 2 mm., which contained translucent, jelly-like material, and small cavities within the basal ganglia, but Stone and Sturdivant [5] reported the first case of a tumor which might have been of surgical significance. In their case there was an irregular excavation at the base of the left temporal lobe, measuring 5 to 6 cm., which was produced by destruction of the cortex. This lesion was unusual in view of the fact that most authors have commented on the absence of cellular reaction to the invasion of the organism and the lack of a destructive process. Rappaport and Kaplan [6] likewise referred to a solid tumor, 2 cm. in diameter, as did Ball.[7] The only other reference to an actual tumor due to infection with histolytica is that by Longmire and Goodwin.[8] In their case an oval area in the left temporal lobe, measuring 3 to 5 cm., had undergone mucinous

1. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916, pp. 1-98.

2. Freeman, W.: Torula Infection of the Central Nervous System, J. f. Psychol. u. Neurol. **43**:236, 1931.

3. von Hansemann: Ueber eine bisher nicht beobachtete Gehirnerkrankung durch Hefen, Verhandl. d. deutsch. path. Gesellsch. (1905), 1906, p. 21.

4. Flu, P. C., and Woensdright, M. G. G.: A Case of Blastomycosis of the Central Nervous System, Mededeel. v. d. Burgerl. geneesk. dienst Nederl.-Indië **6**:1, 1918.

5. Stone, W. J., and Sturdivant, B. F.: Meningo-Encephalitis Due to Torula Histolytica, Arch. Int. Med. **44**:560 (Oct.) 1929.

6. Rappaport, B. Z., and Kaplan, B.: Generalized Torula Mycosis, Arch. Path. **1**:720 (May) 1926.

7. Ball, H. A.: Human Torula Infections, California & West. Med. **32**:338, 1930.

8. Longmire, W. P., Jr., and Goodwin, T. C.: Generalized Torula Infection, Bull. Johns Hopkins Hosp. **64**:22, 1939.

changes. As far as can be ascertained, only 2 cases of torular tumor of the spinal cord have been reported. Smith and Crawford [9] described a granuloma involving the thoracic portion of the cord and the under surface of the dura, with chronic meningitis. This tumor measured 0.25 by 0.5 by 1 cm. Goodhart and Davison [10] reported a case of intramedullary granuloma of the cord with demyelination.

COMMENT

From the review of the literature and from our own experience, it is apparent that T. histolytica may produce space-occupying lesions which occasionally are of surgical significance. The preoperative diagnosis of such a tumor may be most difficult, as it was in case 2. Here, even though there was proved torular infection of the lung, repeated studies of the spinal fluid showed that the cell count and the sugar content were normal and cultures negative for the organism. This indicates that changes in the spinal fluid may not appear for weeks after the onset of symptoms. In typical instances of meningitis, such as 2 cases recently encountered, the organisms could be grown with ease, even on routine culture mediums, from the spinal fluid, as well as from the blood, urine and sputum. Roentgenographic examination of the chest showed no demonstrable lesions in either of these cases or in case 1 of this report. However, we believe roentgenographic examination of the chest is advisable in all cases in which cerebral tumor is suspected and that it may occasionally give a clue to torular infection, as well as to the presence of a malignant growth.

9. Smith, F. B., and Crawford, J. S.: Fatal Granulomatosis of the Central Nervous System, Due to Yeast (Torula), J. Path. & Bact. **33**:291, 1930.

10. Goodhart, S. P., and Davison, C.: Torula Infection of the Central Nervous System, Arch. Neurol. & Psychiat. **37**:435 (Feb.) 1937.

While the lesions may be multiple and a focal diagnosis impossible, a large single granuloma, such as that in case 2, may give a clinical picture of an isolated neoplasm. When the lesion is encountered at operation, the gross appearance is characteristic. At first glance the lesion may resemble a glial tumor; only section of the "tumor" reveals the characteristic appearance of a multiloculated cyst filled with gelatinous material. This "tumor" is unlike true cystic tumors in that the cavities do not empty themselves when opened—the most striking feature of the torular granuloma. In case 2 the mass did not resemble superficially the gelatinous cysts previously described, and the lesion was not recognized grossly because a deep section was not made. A full centimeter of tissue was removed without opening a cyst, and this tissue was rather firm. When the mass is attacked radically, as was done in the second operation, the cyst is encountered, and the gross diagnosis should be obvious.

In addition to the cystic nature of the lesion, the tendency to isolation and sharp demarcation from the adjacent cortex, together with the absence of reaction in the surrounding tissue is a striking feature. This suggests the possibility of radical surgical removal in cases in which there is no meningitis. Such a circumstance, however, must undoubtedly be rare. In addition, there exists the danger that the cyst will be opened unawares and meningitis initiated. We believe that this was done in case 2.

CONCLUSION

In 2 cases of torular infection there developed large granulomatous lesions in the brain which simulated cerebral neoplasms.

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THE SCALENUS ANTICUS SYNDROME

TYPES; THEIR CHARACTERIZATION, DIAGNOSIS AND TREATMENT

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MEDICAL CORPS, ARMY OF THE UNITED STATES

The scalenus anticus syndrome has occurred with unexpected frequency in members of the armed forces of the United States. Its incidence has been sufficiently great to warrant emphasis on the ease with which the syndrome can be recognized and treated. Furthermore, certain observations of both clinical and physiologic importance should be recorded.

Characteristic neurologic signs, consisting of sensory changes, muscular spasm and weakness, were noted among the patients studied. The distribution and nature of these signs, together with their response to appropriate therapy, suggest that they were due to compression of cervical nerve roots. The mechanism by which the lower roots are compressed by the scalenus anticus muscle is fairly well understood, but the means by which the upper roots are compressed needs to be clarified. In an attempt to do this, a detailed anatomic account of the scalene muscles and their pertinent relations will be presented.

For a review of the literature the reader is referred to Murphy,[1] Adson and Coffey[2] and Ochsner, Gage and DeBakey.[3]

ANATOMIC CONSIDERATIONS

The scalenus anticus muscle arises from the anterior portions of the transverse processes of the third, fourth, fifth and sixth cervical vertebrae by well developed tendons (fig. 1).[4] These pass downward and slightly laterally, joining to form a strong muscle, which is inserted into the scalene tubercle on the superior surface of the first rib. Each tendon of origin passes directly in front of, and in close relation with, the cervical nerve root one segment below. These nerves pass laterally and slightly downward in grooves in the anterosuperior surfaces of the transverse processes of the cervical vertebrae. Near the tips of these processes the nerve is directly between the transverse process, which is grooved for it to lie in, and the tendon of origin of the scalenus anticus muscle arising from the transverse process above. Thus, the fourth cervical nerve can be readily pressed on by the tendon arising from the third cervical transverse process, the fifth cervical nerve by the tendon from the fourth transverse process, and so on, so that the fourth to the seventh cervical nerve roots are related to the tendons of origin of the scalenus anticus muscle in the manner described. The fourth and fifth cervical nerve roots are relatively small, and for this reason are probably less vulnerable to pinching. The sixth and seventh roots, however, are large and more easily exposed to direct pressure from the overlying tendons.

The relation of the lower part of the muscle and its insertion to the eighth cervical and first thoracic nerves is more complicated. Directly behind the insertion of the muscle into the scalene tubercle of the first rib runs the subclavian artery. Behind this is the broad insertion of the scalenus medius muscle. This muscle arises in the same manner as the scalenus anticus muscle, but from the posterior tubercles of the transverse processes, the points of origin starting one vertebra above. Its slips of origin join to form a muscle belly which descends in the neck posterior to, and in intimate relation with, the scalenus anticus muscle.

In the interval between the anterior and the medial scalene muscle are the elements which form the brachial plexus. The lower roots of the plexus lie just above the brachial artery, at a point where both of the scalene muscles are held in a relatively rigid position by virtue of their attachment to the first rib. The presence of a long seventh cervical transverse process or a

From the Fifth General Hospital, United States Army.

With the technical assistance of the Physical Therapy Department, Army of the United States, headed by Lieutenant Olena M. Cole, Physical Training Aide, assisted by Lieutenant Edna M. Blumenthal, Physical Training Aide, Army of the United States.

1. Murphy, J. B.: A Case of Cervical Rib with Symptoms Resembling Subclavian Aneurism, Ann. Surg. **41**:399, 1905.

2. Adson, A. W., and Coffey, J. R.: Cervical Rib: A Method of Anterior Approach for Relief of Symptoms by Division of the Scalenus Anticus, Ann. Surg. **85**:839, 1927.

3. Ochsner, A.; Gage, M., and DeBakey, M.: Scalenus Anticus (Naffziger) Syndrome, Am. J. Surg. **28**:669, 1935.

4. The special anatomic observations on the relationships of the scalenus anticus muscle were made at the Anatomical Laboratories, Queens University, Belfast, Ireland.

cervical rib enhances this inelasticity by further immobilizing, and probably also by displacing forward, the scalenus medius muscle. Under normal circumstances there is sufficient space for the scalenus anticus and scalenus medius muscles, and the brachial plexus is not squeezed. Simple hypertrophy or spasticity of these muscles, however, would conceivably cause some concern for

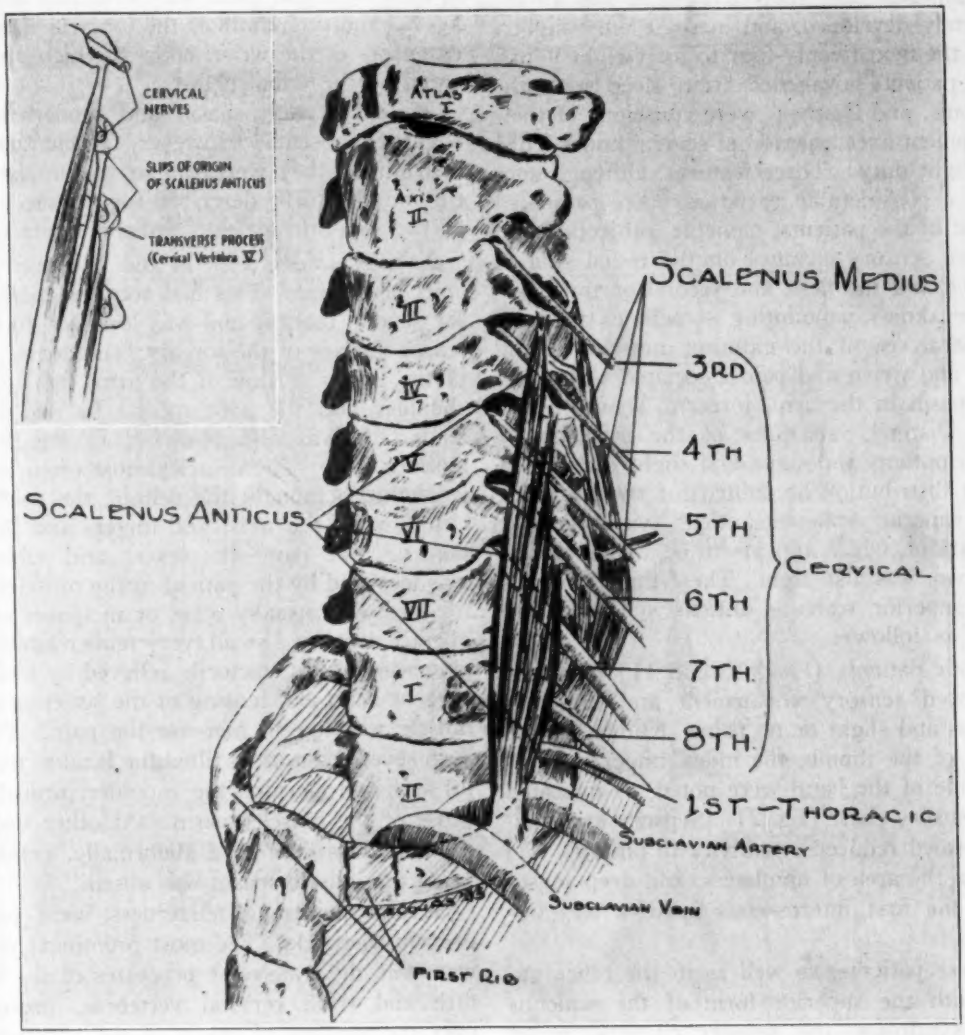

Fig. 1.—A schematic drawing of the cervical and upper thoracic vertebrae, showing the relation of the scalene muscles to the cervical and first thoracic nerve roots, the subclavian artery and vein and the first rib. The insert in the upper left corner shows in greater detail the origin of the scalenus anticus muscle.

the lower roots of the plexus, since the scalenus medius muscle could not retreat dorsally to relieve the pressure. The upper roots of the plexus would probably not be pinched in the same manner because higher in the neck both of the scalene muscles concerned could be displaced freely. These roots, however, are in danger of being compressed by the slips of origin of the scalenus anticus muscle, in the manner already described.

CLINICAL CONSIDERATIONS

With respect to the foregoing anatomic considerations, one should expect to recognize two clinical syndromes attributable in large part to the scalenus anticus muscle, a superior type, due to compression of the upper roots of the brachial plexus, primarily the sixth and seventh cervical roots, and an inferior type, due to compression of the lower roots of the plexus, primarily the eighth cervical and first thoracic roots. This expectation has been realized, as will appear from the analysis of the cases of 15 patients which are reported in this study. The series included 11 young men in the Army of the United States, a middle-aged male Red Cross worker, a young United States Army nurse, a young female Red Cross worker and a young man in the British

Army. In 2 of the patients the syndrome was bilateral, the total number of cases of the syndrome being 17. Nine instances of the syndrome were of the superior and 8 of the inferior type.

Superior, or Upper, Type of the Scalenus Anticus Syndrome.—The onset is usually relatively sudden. Within a period of several hours the symptoms and subjective signs are almost completely developed, and increase only slightly within the next twenty-four to forty-eight hours. Three patients awakened from sleep with the symptoms, and 2 others were conscious of their development over a period of several hours while doing light duty. Three features, although subject to a considerable variation, were presented by most of the patients, namely: subjective and objective sensory changes on the radial side of the hand and the first, and second or third fingers; weakness, amounting sometimes to complete paralysis, of the extensor muscles of the fingers and wrist, and pain associated with muscular spasm in the arm, forearm, shoulder and neck. Distinct variations in the intensity of these symptoms and signs and slight differences in their distribution accounted for two varieties of the superior scalenus anticus syndrome. A third variant, which appears to be a combination of the two, was also seen. These three varieties of the superior scalenus anticus syndrome are defined as follows:

1. Four patients (8, 9, 10 and 11) exhibited pronounced sensory impairment and muscular weakness and slight or no pain. Numbness and tingling of the thumb, the index finger and the radial side of the hand were noted, as indicated in the sensory chart (fig. 2). Sensory examination revealed reduced sensitivity to pinprick and cotton in the area of numbness, and deep sensation in the first interosseous muscles was impaired.

In these patients, as well as in the other patients with the superior form of the scalenus anticus syndrome, the sensory changes varied from day to day in both extent and intensity. In 1 patient the numbness started on the thumb and spread to the index finger and the adjacent dorsal surface of the hand. In another it appeared first on the index finger and later spread to the thumb. In both patients the signs tended to come and go from day to day, but in the individual patient the pattern of spread and of regression of the sensory signs remained constant.

These patients presented wrist drop, and had it not been for weakness of other muscles the condition would have been diagnosed as paralysis of the radial nerve (fig. 3). The wrist drop had developed rather abruptly, as had the sensory changes. Examination revealed some, although less severe, weakness of the flexors of the wrist and fingers, of the pronators and supinators of the forearm and of the intrinsic muscles of the hand and wrist. Little weakness could be demonstrated in the muscles proximal to the elbow, and there was noticeably less weakness of the supinators of the forearm than of the extensors of the wrist, both of which are innervated by the radial nerve.

Muscular pain, spasm and tenderness were slight or absent. However, in character and distribution they were similar to the changes in the muscles to be described for the next variant of the superior scalenus anticus syndrome.

2. In 3 patients (13, 14 and 15) pain was the chief complaint. This had recurred periodically for several months and was localized to the extensor surface of the forearm, the dorsal surface of the upper portion of the arm, the tip of the shoulder and the area medial to the shoulder blade. It was also observed in the posterior axillary fold. The muscles most often involved were the rhomboids, the deltoid, the triceps, the extensors of the wrist and fingers and the teres major. The pain was severe and aching and was localized by the patient in the muscles. The muscles were usually tense or in spasm and frequently contained small, very tender knots. The pain was not satisfactorily relieved by local massage or heat, and tensing of the scalenus anticus muscle was apt to increase the pain. Patients with severe pain often tilted the head to the painful side and elevated the shoulder, probably because of the muscle spasm. At other times the shoulder was depressed abnormally, presumably when the muscle spasm was absent.

Several points of tenderness were palpated deep in the neck. The most prominent of these was over the transverse processes of the fourth, fifth and sixth cervical vertebrae, presumably over the tendons of origin of the scalenus anticus muscle. Another tender spot was deep in the supraclavicular fossa, over the insertion of this muscle. Likewise, the area along the course of the entire muscle was usually tense and moderately tender.

No weakness could be demonstrated in 2 of these patients (13 and 14), although they recalled that weakness had been present from time to time before they entered the hospital. Also, objective sensory impairment could not be demonstrated, although both had noted subjective numbness and tingling of the index and middle fingers from time to time. In addition

to the pain previously noted the third patient (15) exhibited weakness of the triceps and serratus anterior muscles, and to a lesser extent of the extensor muscles of the wrist and fingers. This patient also exhibited a slight decrease in the sensitivity of the index and middle fingers to pinprick and cotton.

In summarizing the observations on the patients with the superior form of the scalenus anticus syndrome, it may be said that the first 4 patients exhibited distinct paralysis and definite sensory changes. They complained only slightly of pain, and muscular spasm could not be demonstrated. In contrast to the syndrome presented

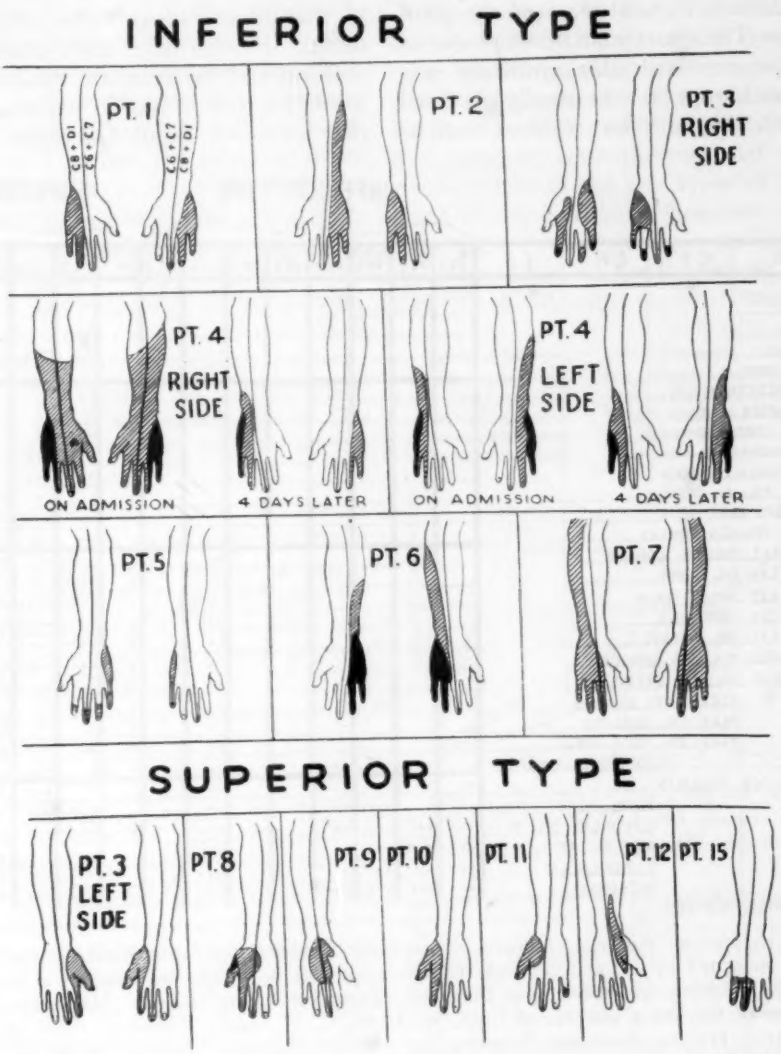

Fig. 2.—Distribution of diminished sensitivity to pinprick and cotton in the inferior and the superior form of the scalenus anticus syndrome. Solid black indicates complete loss of sensation, and cross hatching denotes partial loss. The boundaries of the cutaneous areas of the upper extremity are taken from Monrad-Krohn (Monrad-Krohn, G. H.: The Clinical Examination of the Nervous System, ed. 7, New York, Paul B. Hoeber, Inc., 1938).

3. The last 2 patients with the superior form of the scalenus anticus syndrome (patient 3, left side, and patient 12) exhibited features of both the preceding forms. There was a moderate degree of sensory impairment, muscular weakness and pain, the distribution and character being essentially the same as those already noted for the previous two variants.

by these patients, 3 patients, complained of considerable muscular aching and exhibited pronounced spasms of the painful muscles. They presented no, or slight, paralysis and no, or only slight, sensory changes. Forming a transition between these two forms was the syndrome presented by 2 patients of moderate weakness, moderate pain and muscular spasm and minimal

sensory changes, the distribution and nature of which were approximately the same as those characteristic of the two preceding forms. Pain and muscle spasm appear to be reciprocally related to paralysis and sensory changes. This relation is represented schematically in figure 4. The mechanisms involved will be further considered in the section on "Comment."

Inferior, or Lower, Type of the Scalenus Anticus Syndrome.—The onset and development of symptoms in patients with this syndrome was slow, rather than abrupt, as was usually observed in patients with the superior scalenus anticus syndrome. On admission to the hospital, these patients had experienced symptoms for from four to six weeks. Numbness and tingling in the little and ring fingers were usually noticed first. This disturbance varied in severity from day to day, and noticeable variations were sometimes observed during the same twenty-four hours. After a few days to several weeks the patient noticed clumsiness of the involved hand and frequently dropped things. Later it became evident that his grip was poor, especially that of the little and ring fingers, and that all movements of the hand involving its intrinsic musculature were clumsy. In several patients the weakness preceded the numbness.

As in patients with the superior form of the syndrome, the manifestations of the inferior form consisted of sensory changes, muscular weakness and pain and tenderness. The distribution of these signs, however, corresponded roughly to that of the ulnar rather than of the radial nerve. Furthermore, their character was more uniform and the resultant syndrome more easily identified than it was in patients with the superior form. A detailed account of the manifestations of the inferior type of the scalenus anticus syndrome now follows.

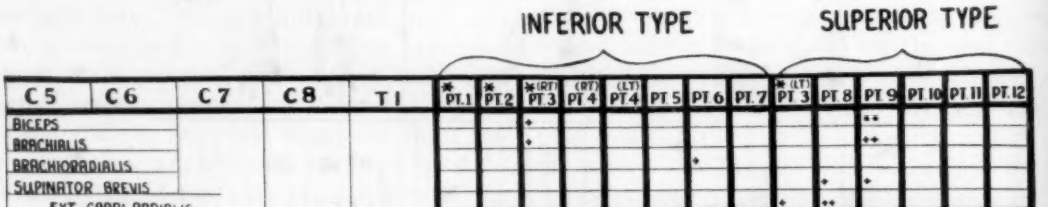

Fig. 3.—This chart shows the relative degree of muscular weakness that was detected in the upper extremity. Slight weakness is indicated by +, and complete paralysis, by + + + +. The nerve supply of the various muscles is also indicated. This scheme was taken from Bing and Haymaker (Bing, R., and Haymaker, W.: Regional Diagnosis in Lesions of the Brain and Spinal Cord, St. Louis, C. V. Mosby Company, 1940), with a few modifications from Morris' Human Anatomy (Morris, H.: Morris' Human Anatomy, edited by C. M. Jackson, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1933).

Sensory Changes: Examination revealed diminished sensitivity to pinprick and light touch along the ulnar border of the hand and the ring and little fingers (fig. 2). In an occasional patient the middle finger and the ulnar side of the forearm were involved. As was noted in patients with the superior form of the syndrome, the development of the sensory changes followed a characteristic pattern. Usually the tip of the little finger became involved first, next the entire

finger and the ulnar border of the adjacent portion of the palm and later the ring finger. Usually no further spread occurred, but in several cases the changes extended up the ulnar side of the forearm and then crept toward the radial side of the hand and later of the forearm. When the sensory changes receded, they did so in inverse order. Variations from day to day were checked objectively; they are illustrated typically by case 4.

Muscular Weakness: There was usually weakness of grip, especially of the ring and little fingers (fig. 3). All movements of the fingers produced by the intrinsic muscles of the hand were weak, and in 1 patient the extensor muscles of the fingers and wrist were involved, but to a less extent. No patient in this group presented as pronounced weakness as did the patients with the superior form of the syndrome. Two patients had flexor deformities of the ring and little fingers, similar to those associated with paralysis of the ulnar nerve, several others, fibrillary muscular twitchings, and another, muscular atrophy of the intrinsic muscles of the hand, accompanied by "trophic" changes in the overlying skin.

Pain: Pain was mild and occasionally absent in these patients, and muscular spasm could not be demonstrated. The character of the pain was the same as that observed in patients with the superior form of the syndrome. Tenderness was usually noted along the entire course of the scalenus anticus muscle, especially over its origin and insertion, but was usually absent elsewhere.

Patient 4 had spontaneous attacks of flushing of the skin accompanied by sweating. These vascular phenomena appeared first on the head, neck and upper extremities and then spread over the rest of the body. They were a part of the syndrome, as was shown by their disappearance after scalenotomy.

Ochsner, Gage and DeBakey [3] observed oscillometric changes in the affected arm of all their patients. We studied the pulse before and after tensing of the scalenus anticus muscle and found it decreased in 4 of 6 patients. In a patient with bilateral involvement the pulse at the wrist disappeared on one side and became barely perceptible on the other. At this point it is important to point out that the scalenus anticus muscle is tensed by the subject's turning the head toward the affected side and lifting the chin. When the head is turned in the opposite direction, other factors become operative, which also weaken the pulse. In fact, we have found that the pulse can be obliterated or weakened in at least half of all normal persons when the head is turned in the opposite direction. In older patients one would have to be sure that the changes in the pulse were not due to the influence of the carotid sinus. Inspiration accentuates the effects on the pulse of tensing the scalene muscle. Study of our cases has shown that there is no relation between the distribution or the severity of changes in the nerve and the ability to affect the pulse at the wrist by tensing the scalene muscles.

Mixed Types of the Scalenus Anticus Syndrome.—Combinations of the upper and lower types of the scalenus anticus syndrome are unusual, but do occur. The syndromes presented by patients 6, 8 and 9 might be considered in this category, since the muscular weakness was characteristic of the two types of the syndrome. Even in these patients, however, the onset and course of the condition and the sensory changes were characteristic predominantly of one or the other type. Another patient,[5] seen recently, appeared to have a true mixed form of the syndrome. Both muscular weakness and sensory changes involved both the upper and the lower roots of the brachial plexus. It is interesting that during the early stages some of the patients with the inferior type of the syndrome manifested muscular weakness more in keeping with the superior type.

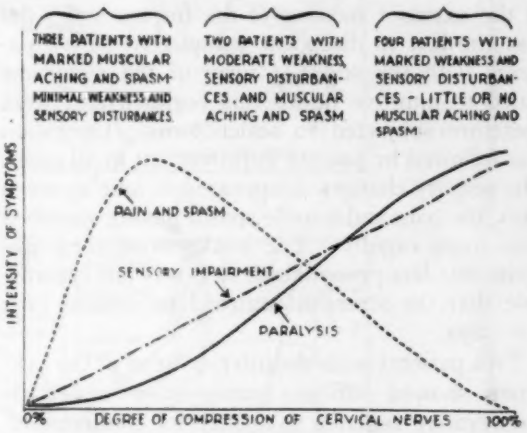
THREE PATIENTS WITH MARKED MUSCULAR ACHING AND SPASM-MINIMAL WEAKNESS AND SENSORY DISTURBANCES
TWO PATIENTS WITH MODERATE WEAKNESS, SENSORY DISTURBANCES, AND MUSCULAR ACHING AND SPASM
FOUR PATIENTS WITH MARKED WEAKNESS AND SENSORY DISTURBANCES - LITTLE OR NO MUSCULAR ACHING AND SPASM
INTENSITY OF SYMPTOMS
PAIN AND SPASM
SENSORY IMPAIRMENT
PARALYSIS
0%
DEGREE OF COMPRESSION OF CERVICAL NERVES
100%

Fig. 4.—Diagram illustrating the relationship of pain and muscle spasm to sensory changes and muscle weakness in the superior form of the scalene anticus syndrome.

It is well to mention here the occasional patient with paralysis of the serratus anterior muscle, thought to be due to pressure on the long thoracic nerve during its passage through the scalenus anticus muscle (Wilson [6]). We have seen 1 patient with this condition. He recov-

5. This patient was British and was transferred from this hospital. As his eventual treatment and the course of his illness are unknown, a complete history and physical examination are not included here.

6. Wilson, S. A. K.: Neurology, ed. 1, London, Edward Arnold & Co., 1940.

ered with conservative treatment. Another patient (15) manifested this paralysis, in addition to the sensory and motor changes of the superior form of the syndrome.

Treatment and Course.—All the patients were first given a course of conservative treatment, lasting ten to fourteen days. This treatment consisted of heat and massage to the neck in the region of the scalenus anticus muscle and, in addition, posturing of the head for one hour three times daily and during sleep at night. For this purpose, pillows were arranged so as to hold the head slightly flexed and inclined toward the involved side, the object being to relieve the tension of the scalenus anticus muscle, as suggested by Reichert.[7] With this treatment the condition of 4 patients with the superior form of the syndrome gradually returned to normal in four to seven weeks. The sensory changes returned to normal in a week or less; the weakness of the extensor muscles of the fingers and wrist was the last to disappear completely. Five patients with the superior form of the syndrome failed to improve under this regimen and were therefore subjected to scalenotomy. Operation was followed by prompt improvement in all cases. The sensory changes disappeared in four to seven days, the pain and muscle spasm having vanished even more rapidly. The weakness of these patients was less pronounced, so it was not remarkable that the strength returned to normal in a few days.

Two patients with the inferior form of the syndrome showed sufficient improvement under the conservative regimen to justify its continuation. They recovered completely in three weeks. Another (patient 6) failed to improve with this treatment during a period of eight weeks. Five patients with the inferior form of the syndrome failed to show improvement while receiving conservative therapy and were therefore subjected to scalenotomy. Four of these patients (1, 3, 4 [right side] and 5) were able to return to full duty ten to fourteen days after the operation. The exception (patient 2) had pronounced muscular atrophy, which improved greatly but was still evident after six weeks of observation. The sensory changes returned to normal in several days. In a few patients, either conservative or operative therapy was followed by an increase in pain for three to four days. Alleviation of the pain was sudden at the end of this time.

Differential Diagnosis.—Ochsner, Gage and DeBakey [8] discussed the differential diagnosis of this syndrome. On the basis of the literature and of many private communications, one may conclude that the mechanism of the inferior form of the scalenus anticus syndrome is usually recognized and the proper therapy administered. It is worthy of note, however, that if the sensory changes are overlooked the condition in some cases might be confused with early progressive muscular atrophy. On the other hand, the superior form of the syndrome appears to have been either overlooked or poorly characterized. Certainly, in the main its relation to the scalenus anticus muscle has been missed. This conclusion is based on a review of the literature and on personal communications with neurologists, neurosurgeons and others concerned with this field. Most commonly this condition has been diagnosed as "myositis" or "myalgia," in spite of the presence of clearcut sensory changes in the hand.

Recently it has been pointed out that herniation of the sixth cervical nucleus pulposus may produce symptoms attributable to pressure on the seventh cervical nerve root (Semmes and Murphey [8]). The clinical picture in cases of this condition is similar to that observed in some of our cases of the superior scalenus anticus syndrome, except that precordial pain was present in the former. The rarity of herniation at this level diminishes its importance in the differential diagnosis, and the results of therapy in our cases were fairly conclusive in ruling it out. The similarity of the two clinical syndromes is of interest and supports the explanation of the symptoms which we offered for the superior scalenus anticus syndrome.

SURGICAL CONSIDERATIONS

The operation for scalenotomy is done through an incision 5 cm. long and 2.5 cm. above and parallel with the clavicle. The medial third of the incision overlies the lateral margin of the sternocleidomastoid muscle. The platysma muscle is divided, and the dissection is carried through the subclavian triangle, with retraction of the external jugular vein medially or laterally and of the posterior belly of the omohyoid muscle upward. The clavicular attachment of the sternocleidomastoid muscle is retracted medially to expose the scalenus anticus muscle; division of its fibers is not necessary. The deep cervical fascia is divided, and the phrenic nerve, along with the internal jugular vein, is retracted medially. After the scalenus anticus muscle is freed of the under-

7. Reichert, F. L.: Compression of Brachial Plexus: The Scalenus Anticus Syndrome, J. A. M. A. **118**:294 (Jan. 24) 1942.

8. Semmes, R. E., and Murphey, F.: The Syndrome of Unilateral Rupture of the Sixth Cervical Intervertebral Disk with Compression of the Seventh Cervical Nerve Root, J. A. M. A. **121**:1209 (April 10) 1943.

lying structures (subclavian artery and roots of the brachial plexus), it may be divided near its tendinous insertion. Care is taken to avoid the cervical reflection of the parietal pleura, which rises, for a distance of 1 or 2 inches (2.5 or 5 cm.) above the upper margin of the sternoclavicular articulation, medial to the scalenus anticus muscle. The disposition of other pertinent anatomic structures should be kept constantly in mind during this dissection.

In the 8 patients undergoing operation (10 scalenotomies), the following abnormalities were noted (fig. 5):

1. Hypertrophy of the scalenus anticus muscle (all patients).

2. Origin of the anterior and middle scalene muscles from a common belly with low division of the two, so that the brachial plexus was compressed between the subclavian artery and the fusion of the two muscles (2 patients; fig. 5 *D*).

3. Passage of the brachial plexus through the substance of the scalenus anticus muscle (2 patients; fig. 5 *B*).

4. Compression of the roots of the brachial plexus by the scalenus anticus muscle against the scalenus medius muscle, which was held forward by a transverse process of the seventh cervical vertebra (3 patients), or compression on both sides by cervical ribs (rudimentary cervical ribs, Gruber's class 1; fig. 5 *C* and *D*; 1 patient).

5. Abnormally broad insertion of the scalenus anticus muscle to the scalene tubercle of the first rib (1 patient).

Little bleeding or oozing was encountered from the cut ends of the muscle, and its proximal portion retracted to above the incision. Care was taken to cut all fibers of the muscle and its sheath, in an attempt to prevent regeneration of the muscle. In 4 patients a section of muscle was removed. It should be mentioned that in cases in which the brachial plexus passed through the substance of the scalenus anticus muscle, the loop of the muscle was sectioned to allow the muscle to retract free of the plexus. The patients were up and about on the first postoperative day and were able to return to full duty, with well

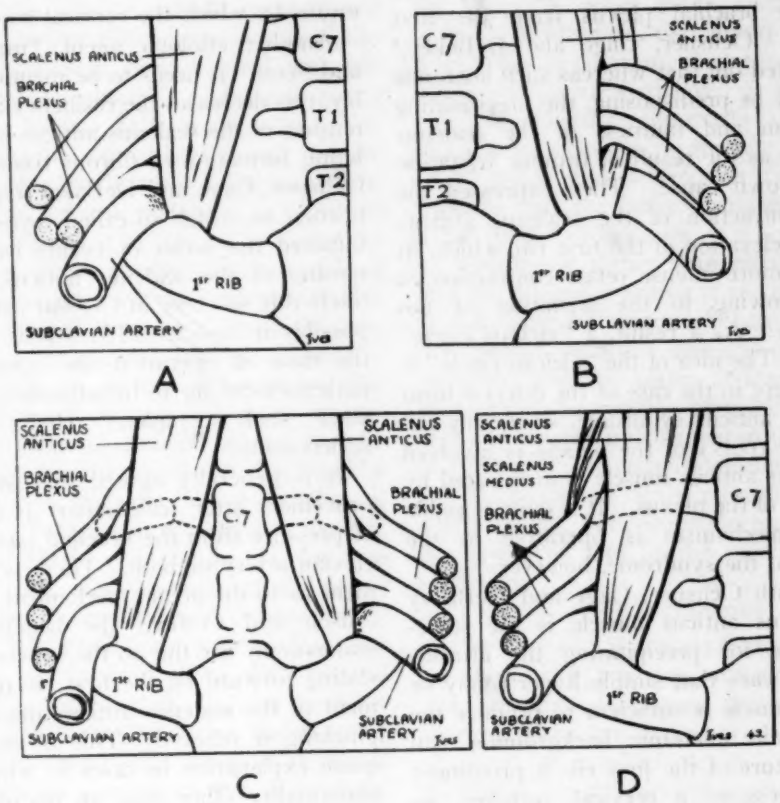

Fig. 5.—Diagrams illustrating the various anatomic relations which were observed during operations. In *A* is shown the constriction of the subclavian artery and the crowding of the trunks of the brachial plexus; in *B*, the brachial plexus passes through a split in the scalenus anticus muscle; in *C* bilateral cervical ribs are represented schematically, and in *D* the scalenus anticus and scalenus medius muscles are represented as arising from a common origin and then splitting to surround the brachial plexus. Note, also, the abnormally long transverse process of the seventh cervical vertebra shown in *D*.

healed wounds, a week or ten days after the operation.

COMMENT

The mechanism of the pinching and irritation of the brachial plexus and subclavian artery which are observed in cases of the scalenus anticus syndrome has been explained in a number of ways. Todd [9] suggested that the angulation and stretching of the brachial plexus were due to a drop in the position of the shoulder, with failure of the sternal portion of the thoracic cage to become correspondingly depressed. Jones [10] suggested that symptoms are produced only in persons who have a large component added to the brachial plexus from the first thoracic root. Ochsner, Gage and DeBakey,[3] however, pointed out that whereas such anatomic conditions may be predisposing, the precipitating cause is spasm and tautness of the scalenus anticus muscle as the result of trauma, irritation or some unknown cause. They expressed the belief that contraction of the scalenus anticus muscle causes elevation of the first rib, which, in turn, leads to more intense reflex contraction of that muscle, owing to the irritation of the brachial plexus. As a result, a "vicious circle" is established. The idea of the "vicious circle" is not easy to accept in the case of the inferior form of the scalenus anticus syndrome, since only the lower root (or roots) of the plexus is involved and the scalenus anticus muscle is innervated by the upper roots of the plexus. It is quite possible that such a mechanism is operative in the superior form of the syndrome, however.

We agree with Ochsner, Gage and DeBakey that the scalenus anticus muscle is the structure responsible for precipitating the attacks. Although it appears that simple hypertrophy or spasm of this muscle is sufficient to produce the syndrome, certain anatomic backgrounds (an abnormal curvature of the first rib, a prominent transverse process of a cervical vertebra, an abnormal origin of the anterior and middle scalene muscles or an abnormal course of the brachial plexus through the scalenus anticus muscle) predispose the patient to the development of the inferior form of the syndrome. Simple hypertrophy or spasm appears sufficient to cause compression of the upper roots also, although it is likely that anatomic relations, not understood at present, aid in the development of the superior form of the syndrome.

The scalenus anticus muscle probably became hypertrophied from overuse in most of the patients whose cases are reported here. This was probably caused by strenuous physical exertion during training. As a result of carrying packs and breathing vigorously, the accessory muscles of respiration, including the scalenes, became hypertrophied. Another precipitating cause, with a similar mechanism, is breathing made difficult by pneumonia (patient 2) or collapse of a lung, due to a gunshot wound in the chest (2 patients).[11] Theoretically, this causes overactivity of the scalene muscles in their function as accessory muscles of respiration. In the latter increased tension, rather than hypertrophy, of the scalenus anticus muscle was probably the means by which the cervical roots were pinched.

Another etiologic agent, "myositis" (Beeson and Scott [12]), needs to be mentioned. Presumably, this decreases the resiliency and increases the tension of the scalenus anticus muscle by stimulating formation of fibrous tissue in the muscle. Ochsner, Gage and DeBakey reported a case of fibrosis in which so-called myositis might have initiated the series of events leading up to the tensing of the scalenus anticus muscle. Very likely this was true in 1 of our patients (14), and possibly in another (13). It is unlikely that at the time of operation the symptoms of these patients were due to inflammation of the muscles, since such complete relief occurred after scalenotomy.

It is generally agreed that symptomatic improvement after scalenotomy is due to removal of pressure from the brachial plexus or the subclavian artery or both. There is some disagreement as to the actual mechanism. According to Adson and Coffey,[2] the beneficial effects of scalenotomy are due to the subclavian structures sliding forward on the first rib over the attachment of the scalenus anticus muscle so that the pinching is relieved. This is probably an adequate explanation in cases in which there is no abnormality other than an unduly broad costal attachment of the scalenus anticus muscle. In 1 of the patients in our series this condition existed on only one side.

Ochsner and his collaborators proposed a more elaborate and interesting theory. They asserted that the first rib drops after scalenotomy, so that the pressure on the subclavian artery and/or the brachial plexus is relieved. The "vicious circle"

9. Todd, T. W.: The Descent of the Shoulder After Birth, Anat. Anz. **12**:257, 1912.

10. Jones, F. W.: The Anatomy of Cervical Ribs, Proc. Roy. Soc. Med. (Clin. Sect.) **6**:95, 1912.

11. These patients were observed recently. In the case of 1 man follow-up studies are not available, and in the other the symptoms were never severe and subsided spontaneously.

12. Beeson, P., and Scott, T. F. M.: Clinical, Epidemiological and Experimental Observations on an Acute Myalgia of the Neck and Shoulders: Its Possible Relation to Certain Cases of Generalized Fibrositis, Proc. Roy. Soc. Med. **35**:733, 1942.

is thus broken. We have not observed a drop in the first rib after scalenotomy. To be sure, our operations were done with local anesthesia, and a little procaine was injected into the muscle. This may have relaxed the muscle before it was divided. However, fluoroscopic examination after unilateral scalenotomy in 2 of our cases showed no change in the position of the first rib relative to the rest of the thoracic cage. It is unlikely that the scalenus anticus muscle in the adult is responsible for significant independent motion of the first rib.

The relief of symptoms in all our cases was due, we think, to the removal of the ventral component of the vise in which roots of the brachial plexus and/or the subclavian artery are caught. It has already been pointed out that the scalenus anticus muscle is a common factor in forming the ventral half of the vise. The structure forming the dorsal half varies. In the superior type of the syndrome it is the transverse processes of the cervical vertebrae, whereas in the inferior syndrome it is the scalenus medius or part of the scalenus anticus muscle. A long transverse process or a cervical rib contributes to the production of symptoms by fixing the scalenus medius muscle so that it cannot be displaced dorsally to relieve pressure on the lower cervical nerve roots. Spasm or hypertrophy of the scalenus anticus muscle thereby effectively squeezes the roots of the brachial plexus, much as a carpenter's vise squeezes a piece of wood. Such a concept clarifies the role of the cervical rib in contributing to, but not materially altering, the symptoms of the lower type of the scalenus anticus syndrome. This is illustrated by the studies on patient 3 in our series and on a series of patients with cervical ribs reported by Stopford.[13] It also explains the relief of symptoms following scalenotomy, since this procedure removes the ventral jaw of the vise, so that the vise mechanism is rendered ineffective.

The diagnosis depends primarily on the neurologic examination. The most important signs are sensory changes which appear to involve the peripheral part of the sensory segments of the cervical nerves, together with weakness, pain and/or spasm of the muscles innervated by the same nerve roots. Function is impaired in the large, more sensitive, nerve fibers, yet appears never to be completely abolished. These facts suggest that the nerves are only partially compressed. Interestingly, we have observed no apparent effect on sweating, although no sweating tests were undertaken. If our gross observation concerning sweating is correct, the absence of any effect is probably due to sparing of the small nerve fibers subserving the function of sweating. This accords with our concept of partial compression of the cervical nerve roots.

Severe pain was present in only 3 patients, all with the superior form of the syndrome. Mild or vague pain was present in nearly all the remaining patients. In all patients it was dull and aching and was localized in the muscles. Because of the associated muscle spasm, it is likely that this pain was due to muscle spasm rather than to pressure on the sensory nerve fibers. Assuming that the nerve roots (cervical) are but partially compressed, one would not expect pain from pressure on them, since the fibers are small and would be affected late. It is apparent that a reciprocal relationship exists between weakness and sensory changes, on the one hand, and muscular spasm and aching, on the other. This suggests that the latter symptoms are due to a lesser degree of pressure, i. e., one which might be stimulating rather than paralyzing. In this case the muscular aching is secondary to, or due to, the muscular spasm. When the compression is increased, paralysis develops or becomes more complete, and the spasm and aching disappear. In figure 4 the relation of muscle spasm, weakness and sensory impairment in the superior form of the scalenus anticus syndrome and the suggested mechanism of their cause are represented schematically. The same mechanisms are probably operative also in the inferior form of the syndrome.

CONCLUSIONS

The cases of 15 patients with a condition diagnosed as the scalenus anticus syndrome are classified into two main groups: those of a superior type due to compression of the upper roots of the brachial plexus, principally of the sixth and seventh cervical nerves, by the tendons of origin of the scalenus anticus muscle, and those of an inferior type, due to compression of the lower roots of the brachial plexus, principally of the eighth cervical and the first thoracic nerve, by the same muscle near its insertion.

The mechanism of compression is thought of as a vise, the ventral jaw of which is the scalenus anticus muscle. The structure forming the dorsal jaw varies. Section of the scalenus anticus muscle removes the ventral jaw of the vise and renders the vise ineffective.

The etiologic factor in most cases seemed to be hypertrophy of the scalenus anticus muscle. Strenuous exercise and overactivity of the respiratory muscles appeared to be the most important causative factors in this hypertrophy.

13. Stopford, J. S. B.: Compression of the Lower Trunk of the Brachial Plexus by a First Dorsal Rib, Brit. J. Surg. **7**:168, 1919-1920.

In a few cases the syndrome may have been precipitated by "myositis" or "myalgia."

Seven of the patients were relieved by a regimen of rest, posture and physical therapy; 8 (2 with a bilateral syndrome) were relieved by anterior scalenotomy.

REPORT OF CASES

CASE 1.—A man aged 24 two months before admission noticed numbness and tingling along the ulnar side of the left hand. This lasted but a few days and returned two weeks later, accompanied by weakness of the hand. In a few days the weakness disappeared, only to reappear five days before his admission to the hospital. During the three weeks before admission the fourth and fifth fingers were slightly deformed, as a result of hyperextension of the first phalanges and flexion of the terminal phalanges. Spontaneous twitchings of the flexor muscles were often noted in these fingers.

Examination revealed that the patient was well developed and apparently stable. There were slight flexor deformity of the type seen with paralysis of the ulnar nerve and weakness on flexion of the fourth and fifth fingers of the left hand. There were also weakness of abduction and adduction of the fingers and weakness of adduction of the thumb. There was decreased appreciation for pinprick and cotton on the palmar and dorsal surfaces of the fourth and fifth fingers and on the ulnar side of the hand. Roentgenographic studies revealed no cervical rib, but the right transverse process of the seventh cervical vertebra was unusually long. Tensing of the left scalene muscles caused no noticeable change in the pulse but was attended by slight elevation in the diastolic pressure, which reduced the pulse pressure by 25 per cent.

One week after admission, after physical therapy had failed to produce improvement in the patient's condition, a scalenotomy was performed on the left side. At operation the left brachial plexus was found to pass into the neck through a small split (3 cm. in length) in the scalenus anticus muscle (fig. 5 *B*). The plexus emerged at a level in the muscle approximately opposite and above the transverse processes of the seventh cervical vertebra. The ventral slip of the muscle, which covered the plexus, was resected, and the rest of the muscle was divided just above its tendinous insertion in the first rib. The subclavian artery appeared grossly normal. No organic evidence of constriction was detected in spite of the fact that before operation there was a distinct drop in pulse pressure on the left side when the scalenus muscle was tensed. Five days after the operation the patient said that his condition was much improved. Sensory appreciation was normal except in a narrow zone along the ulnar margin of the little finger. The deformities of the fingers had practically disappeared. One week later the patient stated that his condition was normal, and he was discharged to return to duty. A check-up examination two months later revealed no return of symptoms.

CASE 2.—A man aged 23, while convalescing from "atypical" pneumonia, noted weakness and wasting of his right hand. The following day he noted numbness and tingling along the ulnar border of the right hand.

Examination revealed moderate atrophy of, and many muscular fibrillations in, the thenar, hypothenar and interosseous muscles. There were also slight flexor deformities, similar to those in case 1, in the fourth and fifth fingers, and the grip, especially in the fourth and fifth fingers, was weak. Abduction and adduction of the fingers and adduction of the thumb were also weak. Sensitivity to pinprick was impaired over the fourth and fifth fingers and on the ulnar side of the hand and the arm to the elbow. When the scalenus anticus muscle was tensed, the radial pulse was obliterated. A roentgenogram revealed no abnormality of the cervicodorsal portion of the spine.

Scalenotomy was performed on the right side twelve days after symptoms were first noted by the patient. It was evident from the degree of atrophy, however, that the syndrome had been present much longer. At operation, the right brachial plexus was seen to emerge from between two muscle bellies arising in common from the upper cervical transverse processes (fig. 5 *D*). The more medial and ventral belly was identified as the scalenus medius muscle. The split in the muscle was opposite the transverse processes of the fifth and sixth cervical vertebrae. The transverse process of the seventh cervical vertebra felt abnormally prominent, and the lower roots of the brachial plexus were crowded against it by the subclavian artery and a much thickened belly of the anterior scalene muscle. Upward displacement of the roots of the plexus was prevented by a low split in the bellies of the scalene muscle. After the anterior scalene muscle had been sectioned through the tendinous insertion of the muscle, no gross abnormality could be detected in the subclavian artery.

Nine days after operation the patient's strength had greatly improved. The sensory impairment was limited to the ulnar margin of the little finger and the hand. Seven weeks later sensations were normal, and the patient's strength had greatly improved. Some atrophy of the hand was still present, although much less than before operation.

CASE 3.—A man aged 21 four weeks before admission noticed numbness in the ends of the fourth and fifth fingers of the right hand. This gradually spread to the ulnar side of the palm and dorsum of the hand. Finally, the tip, and later the body, of the index finger became involved. During this period the patient noticed that his right hand was weaker, and he was conscious of dropping many things. For two weeks there had been a dull ache along the lateral aspect of his right arm.

Examination revealed that the patient was well developed and stable. Hypalgesia and hypesthesia were noted along the ulnar side of the right hand and the tip of the right index finger, as indicated in figure 2. There were also weakness of flexion of the hand, especially of the fourth and fifth fingers, weakness of adduction and abduction of the fingers and weakness of adduction of the thumb. Tensing the right scalenus muscle caused the pulse to diminish notably on the right side. A roentgenogram of the cervicodorsal region revealed a small cervical rib on the left side and a long transverse process of the eighth cervical vertebra on the right side, with a rudimentary cervical rib.

Physical therapy failed to produce improvement. Six days after admission scalenotomy was performed on the right side. At operation the right scalenus anticus muscle appeared considerably hypertrophied. It had a broad attachment to the scalene tubercle of the first rib, so that the subclavian artery passed unusually high into the neck, with displacement of the lowest trunks of the brachial plexus upward. These trunks were seen to exhibit a pulsation transmitted from the subclavian artery. In addition, the transverse process of the seventh cervical vertebra was abnormally prominent, both ventrally and laterally. The upper trunks of the brachial plexus were compressed against this bony prominence by the taut scalenus anticus muscle. A distinct notch-

ing in these trunks was apparent grossly under the anterior scalenus muscle at the level of the prominent transverse process. After scalenotomy, the subclavian artery dropped medially and inferiorly, with release of the lower elements of the plexus, but the notching in the upper trunks persisted.

Nine days after the operation only slight weakness remained. Sensation had also improved and was normal except for numbness on the tip of the index finger. Seven weeks after operation both sensation and strength were normal.

Four weeks after discharge the patient began to have pain on the radial side of the dorsum of the left hand, and several days later numbness appeared on the end of the left thumb and spread up the thumb to involve the adjacent dorsal surface of the hand and the radial side of the index finger. This pain was relieved somewhat by elevation of the hand over the head. The right hand was asymptomatic except for slight numbness of the tip of the index finger, which later disappeared.

The patient reentered the hospital forty days after his discharge. Examination revealed normal strength and sensitivity in the right hand. On the left side there were slight weakness of the extensors of the wrist and of the fingers and diminished sensitivity to pinprick and cotton on the thumb, the radial side of the index finger and the radial side of the palm on the dorsal, as well as the palmar, surface. Tension on the left scalenus muscle did not alter the pulse rate.

Three days after admission a scalenotomy was performed on the left side. At operation it was observed that the scalenus anticus muscle on this side was not as hypertrophied as it was on the right side. Its attachment to the first rib was not as broad. The uppermost part of the trunk of the brachial plexus was entirely free. The lowermost portion of the trunk was likewise relatively free, but the midportion of the plexus was compressed by the scalenus anticus muscle as it passed over the prominent transverse process and the rudimentary rib of the seventh cervical vertebra (fig. 5 *C*). This became apparent especially after the muscle had been severed. Pressure with the finger against this portion of the plexus caused severe pain in the left hand, but the patient was unable to localize it to any specific part of the hand. The subclavian artery on this side was compressed against the first rib and was narrowed in its second portion. Its wall was roughened in the area where it was crossed by the scalene muscle, and gross narrowing of the vessel persisted after the scalenotomy. It is notable that in this patient no change in the pulse pressure of the brachial artery had been detected when the scalenus anticus muscle was tensed. After operation sensation and strength returned to normal and remained so for the four weeks of observation.

Case 4.—A man aged 24 seven weeks before admission noted weakness, stiffness and tingling in the ring and little fingers of the right hand. Two weeks later the ulnar side of the hand and of the forearm to the elbow began to ache. One week before admission the patient noticed similar sensations and pain in the left hand. They lasted about three days and then disappeared. During this time the patient also noted occasional spontaneous attacks of flushing and sweating. These appeared first on the face and neck and spread to the hands, and to a much less extent to the trunk and the lower extremities.

Examination revealed that the patient was well developed and well nourished and apparently stable. There were weakness of the grip of the right hand, especially of the ring and little fingers, and weakness of adduction and abduction of the fingers and adduction of the thumb. The thenar and hypothenar eminences were slightly atrophic. There was no evident weakness of the left hand. Over both the right and the left upper extremity sensitivity to pinprick and cotton was diminished, as indicated in figure 5. The radial pulse on both the right and the left side was obliterated when the corresponding scalenus anticus muscle was tensed. Roentgenographic examination revealed no cervical rib.

One week after admission the patient's strength and the sensory changes had improved (fig. 2, patient 4, on admission and four days later). Several spontaneous attacks of sweating had been observed. They occurred as described in the history; the sweating was profuse over the face and neck, and the flushing was pronounced. Several days later all symptoms, including weakness and decreased sensitivity, had increased in severity. It was therefore decided that section of the right scalene muscle was indicated.

At operation, sixteen days after admission, the right brachial plexus appeared free, and its relations to the scalenus anticus and the scalenus medius muscle were normal. The subclavian artery, however, was conspicuously compressed (fig. 5 *A*) and angulated under and around the tendinous insertion of the scalenus anticus muscle to the first rib. The inferior elements of the brachial plexus followed the course of the artery lying directly beneath and adjacent to it. The area of constriction in the brachial artery persisted after the scalenus anticus muscle was divided and had retracted up into the neck.

Two days after section of the right scalenus anticus muscle, sensations in the right hand and arm had become normal, and the patient's strength had greatly improved. The attacks of sweating and flushing now originated on the left side of the body and spread from there to the right side, where the intensity was greatly diminished. As the sensory changes persisted on the left side, section of the left scalenus anticus muscle was performed, twelve days after operation on the right one.

At operation the left scalenus anticus muscle was observed to arise as a large common belly with the scalenus medius muscle (fig. 5 *D*). The brachial plexus emerged from between these two muscle bellies and appeared compressed, inasmuch as the nerve trunks were not freely movable between the scalene muscles. The attachment of the scalenus anticus muscle was broader than usual. In addition, the first rib on this side appeared more sharply curved, so that the lower trunks of the brachial plexus were compressed between it and the subclavian artery. After division of the attachments of the scalenus anticus muscle to the first rib, distinct narrowing of the second portion of the subclavian artery was noted, with a suggestion of dilatation distal to this.

One week after the second operation all sensations were normal on the left side, as well as on the right, and the sweating spells had entirely disappeared. Two and a half months later the patient stated that he was entirely normal.

Case 5.—A man aged 36 one month before admission to the hospital had pain in his right elbow. Soon after, pain and apparent weakness appeared in the extensor muscles of the right forearm. During the week before admission the patient noticed that the fourth and fifth fingers of his right hand flexed involuntarily and that his writing was unsteady.

Examination revealed that he was well nourished and stable. There were weakness of the grip of the right hand, especially of the fourth and fifth fingers, and

weakness in adduction and abduction of the fingers. There was also slight weakness of the extensors of the fingers and wrist, and a number of muscular fibrillations were noted in the muscles which produce these movements. Sensitivity to pinprick and cotton was reduced along the ulnar side of the palm and at the tips of the second, third and fifth fingers. A roentgenogram of the cervical portion of the spine revealed nothing abnormal.

The patient received heat and massage to the region of the scalenus anticus muscle. For about four days this therapy intensified the pain in the extensor muscles of the forearm, but thereafter some relief occurred. One week later muscular strength had returned almost to normal, and the sensory changes had become confined to the ulnar side of the little finger and the adjacent portion of the palm. The muscular pain had also subsided. One week later the patient considered himself normal, and all tests for objective sensory and motor changes gave normal results.

CASE 6.—A man aged 22 one month before admission noted weakness in the right hand and numbness in the fourth and fifth fingers of the same hand. These symptoms appeared rather suddenly and remained practically unchanged until his admission to the hospital. More recently he had had cramps in the right hand, with twitchings of the fingers and violent fibrillations or twitchings in the first interosseous muscle. During these attacks he was able to straighten his fingers, but they assumed their flexed position again.

Examination revealed diminished grip in the right hand, especially of the ring and little fingers, moderate weakness of the extensors of the wrist and fingers and weakness of the supinators and pronators of the forearm. Sensitivity to pinprick and cotton was diminished along the ulnar side of the right hand and arm and on the fourth and fifth fingers of that hand. A roentgenogram of the cervicodorsal portion of the spine showed nothing abnormal.

Heat and massage were applied to the region of the right scalenus anticus muscle, and the patient was instructed to sleep with his head flexed and inclined toward the paralyzed side. This posture was also assumed three times daily for one hour. No improvement occurred. At the end of two months no increase in strength was noted. Furthermore, uniform weakness of the entire right upper extremity developed, presumably due to disuse.

CASE 7.—A man aged 22 had been working long hours cutting hair, an occupation which necessitated his keeping his arms elevated a good deal of the time. Two weeks before admission he noted numbness along the ulnar side of the left hand, which appeared toward the end of each day but was absent in the morning. Several days later this numbness became permanent. It extended along the ulnar side of the hand, forearm and arm to the shoulder. Except for slight muscular ache there was no pain.

Examination revealed slight flexor weakness of the fourth and fifth fingers and questionable weakness of the interosseous muscles of the left hand. There was diminished sensitivity to pinprick and cotton along the ulnar side of the arm, forearm and hand and of the third, fourth and fifth fingers on the left side. Four days later his strength had improved, and the sensory impairment had diminished. One week later only slight subjective numbness to pinprick was present along the ulnar side of the forearm, and his strength was normal. A roentgenogram of the cervicodorsal portion of the spine was normal.

CASE 8.—A man aged 21 three days before admission awoke with a wrist drop on the left side and a feeling of numbness at the base of the left thumb. He had been drinking the night before. These symptoms gradually increased until his admission to the hospital.

Examination revealed that he was well developed, well nourished and stable. There was complete paralysis of all the extensors of the wrist and fingers of the left hand. Supination with the elbow extended was weak, but not absent. There was moderate weakness of the abductors and adductors of the fingers and of the adductors of the thumb, as well as of the hand. Above the elbow there was slight weakness of the flexors. Sensitivity to pinprick and cotton was absent over the first metacarpophalangeal joint and was diminished over the rest of the thumb, the dorsal surface of the index finger and the radial margin of the dorsal surface of the hand. Deep muscle sense was impaired in the first interosseous space. Tensing of the scalenus anticus muscle did not alter the pulse. Roentgenographic studies of the cervicodorsal portion of the spine revealed nothing abnormal. Five days after admission sensory changes were present over only a small area of the thumb, and the muscle sense was normal in the first interosseous space. There was also marked improvement in the strength of muscles innervated by the median nerve. Twelve days after admission the paralysis of the radial nerve was still pronounced. The median nerve appeared to have recovered completely, and the ulnar nerve showed slight weakness. Five weeks after admission only slight palsy of the radial nerve remained, and one week later the patient was returned to duty.

CASE 9.—A man aged 20 one week before admission awakened from a short sleep with pronounced weakness of his right arm, forearm and hand. During the next few days the arm gained in strength, but the condition in the forearm and hand remained the same. At first there appeared to be complete cutaneous insensitivity, but in several hours this had changed to partial loss of sensitivity.

Examination revealed that he was well developed and apparently stable. A wrist drop was present on the right side. There were moderate weakness of the flexors and slight weakness of the extensors of the elbow. There was almost complete paralysis of the extensors of the hand and wrist and of the pronators of the forearm. The supinators were moderately weak. All intrinsic muscles of the hand were very weak. There was decreased sensitivity to pain, temperature and light touch sensation on the radial side of the dorsal surface of the hand, and deep muscle sense was impaired in the first and second interosseous muscles.

Two weeks later strength had greatly improved, and cutaneous sensitivity was normal. At this time pressure on the first and second interosseous muscles dorsally still evoked a peculiar sensation of numbness. Two weeks later the strength was practically normal, and sensations were completely normal.

CASES 10 and 11.—Two men aged approximately between 20 and 25 were observed at the Camp Edwards Station Hospital. The histories relative to their complaints were brief. One awakened from sleep with an obvious wrist drop; in the other wrist drop developed over a period of several hours during the day. Closer observation revealed complete paralysis of the radial nerve, moderate paralysis of the muscles innervated by the median nerve and slight weakness of the muscles innervated by the ulnar nerve. The sensory changes consisted of decreased sensitivity to pinprick and cotton

on the dorsal surface of the thumb, the index finger and the radial half of the hand.

With conservative treatment, one patient improved rapidly to complete recovery in five weeks, and the illness of the other had a more prolonged course, complicated by hysterical paralysis. Eventually the paralysis subsided, the entire period of convalescence being approximately ten to twelve weeks. In neither case was cervical rib demonstrable roentgenographically.

CASE 12.—A man aged 38, a Red Cross worker, first noticed a dull ache in the shoulder, arm, forearm and periscapular region of the right side. The following day he was struck in the back with a blunt object. The blow left no evidence of injury, but on the next day he noticed that the pain, which had been dull and aching, became much more severe. Several days later he entered a hospital, where the diagnosis of myositis was made. Examination revealed spasm of the muscles of the right shoulder and the right periscapular region, which was not relieved by heat and massage. A 1 per cent solution of procaine hydrochloride was injected into the spastic muscles, with relief of pain in the back, but similar treatment did not alleviate the pain in the forearm or the arm. The pain continued, and the patient was readmitted to the hospital. At this time he complained of pain in the extensor muscles of the forearm, the arm, the shoulder and the region medial to the scapula, all on the right side. The shoulder was elevated and the head tilted toward it. The muscles involved were spastic, and there was nuchal tenderness along the line of the scalenus anticus muscle. There was an area of diminished sensitivity to pinprick and cotton on the radial margin of the palm, which included the index finger, but not the thumb. This varied from day to day and sometimes even involved the thumb. There was also slight, but definite, weakness of the extensor muscles of the fingers and wrist. Two weeks of rest in bed, with conservative therapy, relieved the pain almost entirely. Several days after the patient had been discharged from the hospital the pain reappeared. He was readmitted, and a scalenotomy was performed on the right side. Complete relief from all symptoms and restoration to normal of sensations and strength were immediate, and the patient returned to full work in two weeks from the date of operation. Occasional contact with this patient for six months has revealed no recurrence of symptoms.

At operation the right scalenus anticus muscle appeared greatly enlarged and rather taut. It was divided near its tendinous portion and a piece resected for biopsy. No other gross abnormality was discovered.

CASE 13.—A woman aged 27 for some years had suffered from recurrent attacks of stiff neck, frequently associated with numbness in the middle and ring fingers of the right hand. Approximately six months before admission to the hospital a 1 per cent solution of procaine hydrochloride was injected into painful nodules in the periscapular muscles. This had given her considerable temporary relief from pain. In addition, she had been treated with heat and massage for several weeks at a time, on a number of occasions, with only slight temporary benefit.

Examination revealed that the head was inclined to the right and the right shoulder elevated. There were pronounced muscle spasm and tenderness in the neck in the region of the scalenus anticus muscle, in the periscapular muscles, the deltoid muscle and the extensor muscles of the forearm. There was little, if any, weakness, and no objective sensory changes were apparent. In the painful, tense muscles were a number of palpable nodules.

Since conservative treatment had failed to give relief, a scalenotomy was performed on the right side. Operation revealed that the right brachial plexus passed through the substance of the scalenus anticus muscle, rather than beneath it (fig. 5*B*). The muscle was divided near its tendinous portion, and the fibers passing behind the plexus were resected. The patient experienced almost immediate relief and has remained free from symptoms for the past six months. There has also been notable improvement in her posture.

CASE 14.—A woman aged 28 had a history practically identical with that of the preceding patient, except that the total duration of the disease was only about fifteen months. During this time the condition had been considered "myositis." The recurrent attacks of pain appeared suddenly and lasted one or two weeks. They were associated with tilting of the head to the right and elevation of the right shoulder. Painful nodules had frequently been observed in the tense and painful muscles, the same muscles as those noted in case 13, except for the inclusion of the teres major muscle.

The patient received conservative therapy for ten days. Occasional intervals of freedom from pain, associated with drooping, rather than elevation, of the right shoulder, were observed during this period. No definite muscular weakness or sensory changes could be demonstrated.

In the main, the symptoms were not relieved, and a scalenotomy was performed on the right side. At operation the scalenus anticus muscle appeared moderately enlarged and taut. The subclavian artery and the brachial plexus seemed grossly normal. Pressure over the plexus in the region of the transverse processes of the lower cervical vertebrae, however, reproduced the pain in the arm and shoulder. The muscle was divided near its tendinous portion, and a segment was removed for biopsy. For a period of five months, up to the time of writing, this patient has been greatly improved. In this case, as in case 13, it is felt that "myositis" probably precipitated the syndrome.

CASE 15.—A man aged 32, a British soldier, noted gradual onset of pain around the right scapula, over the tip of the right shoulder and in the extensor muscles of the right arm and forearm. This was followed by weakness of extension of the forearm and of finer movements of the fingers. The pain was severe and was described by the patient as a tightening of the muscles. There was also numbness of the index and the middle finger. He entered the hospital five weeks after onset of the pain.

Examination revealed reduced sensitivity of the index and middle fingers to pinprick and cotton. There was also weakness of extension of the wrist and fingers, of the triceps muscle and of the serratus anterior muscle, all on the right side. Spasm and tenderness were noted in the painful muscles. A roentgenographic study revealed no cervical ribs. Twenty-five days after admission physical therapy had given little relief; so a scalenotomy was performed on the right side. The scalenus anticus muscle was very tense and hypertrophied, and when cut it retracted well out of sight. For four days after the operation there was some pain, but on the fifth day this disappeared, and a day or so later the sensory changes cleared. Two weeks after the operation the patient was completely free of pain, and his strength had returned to normal. Several days later he was returned to duty.

EFFECT OF GLUTAMIC ACID AND OTHER AMINO ACIDS ON MAZE LEARNING IN THE WHITE RAT

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Price, Waelsch and Putnam [1] have recently reported that *dl*-glutamic acid hydrochloride may be used as an adjuvant in the treatment of petit mal seizures of epileptic patients who are otherwise resistant to anticonvulsant therapy. They found that the administration of the racemic glutamic acid hydrochloride decreased the number of seizures. These investigators also reported a "universally increased mental and physical alertness" in the patients so treated and noted that the "degree of improvement in mental efficiency could not be correlated with the incidence of seizures." On the basis of these clinical observations, it appeared of interest to investigate in detail the effects of glutamic acid and its derivatives on the learning ability of the white rat. However, it must be kept in mind that the experiments reported in the following study were not designed to reproduce the changes observed in the patients, but, rather to demonstrate the effect of ingestion of this compound on maze learning in the normal rat.

This study was divided into two major experiments: Experiment 1 deals with the effect of *dl*-pyrrolidine carboxylic acid, neutralized *dl*-pyrrolidine carboxylic acid and aminoacetic acid; experiment 2, with the effect of naturally occurring *l*-glutamic acid.

EXPERIMENT 1

The first plan was to make use of the *dl*-glutamic acid hydrochloride, which had been used in the experiment on patients. However, it was found in preliminary experiments that rats would not eat any food mixture containing this substance. A derivative of this amino acid, *dl*-pyrrolidine carboxylic acid, was found to be acceptable to the rats and was therefore administered with the food. Since the unnatural (*d*) isomer of the *dl*-pyrrolidine carboxylic acid would be excreted to a large extent [2] and would, consequently, act as a stable acid in the body, another group of rats were given *dl*-pyrrolidine carboxylic acid neutralized with equimolar amounts of sodium bicarbonate. A third group of rats were fed aminoacetic acid with their food. This amino acid is not known to have any particular relation to brain metabolism. A fourth group of rats served as controls and were given only the basic food.[3]

Apparatus.—The Warner-Warden linear maze,[4] an enclosed, or alley, maze, was selected because of its high reliability for study of maze learning. Jackson [5] reported a reliability of 0.91 to 0.98 (Spearman-Brown corrected coefficient). The maze pattern used in the experiment is shown in figure 1. As will be seen, the maze was arranged in a simple left hand alternation pattern of six cul-de-sacs and six true pathway elements. It was mounted on a large table, 6½ by 8 feet (192 by 244 cm.), with the surface 20 inches (50.8 cm.) from the floor. A Westinghouse 16 inch (40.6 cm.), direct current electric fan, run at maximum speed, was used as a sound screen to eliminate incidental noises. A 200 watt bulb in a milk glass globe, placed directly over the table, provided the sole illumination. The one window in the room was shielded by a black blind. The observer maintained a position which eliminated shadows cast on the table while the rats were running the maze.

Subjects.—The subjects of this experiment were male albino rats 6 weeks old. The rats (Sherman strain) were secured from the Rockland Farms, Inc., New City, and from the Department of Animal Care, Columbia University College of Physicians and Surgeons. In order that the complicating factors of the estral cycle might be avoided, only male rats were used.

The rats were divided as follows: (1) group fed *dl*-pyrrolidine carboxylic acid, 29 rats; (2) group fed neutralized *dl*-pyrrolidine carboxylic acid, 16 rats; (3) group fed aminoacetic acid, 20 rats, and (4) control group, 22 rats.

Preliminary Treatment.—Immediately on arrival in the laboratory, the rats were weighed and placed in living cages in groups of 5. For the next three days they were fed the basic food only and were permitted to become accustomed to the living conditions of the laboratory. The rats were weighed and fed once daily,

From the Department of Neurology, Columbia University College of Physicians and Surgeons; and the Animal Laboratory, Department of Psychology, Columbia University.

1. Price, J. C.; Waelsch, H., and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in the Treatment of Petit Mal and Psychomotor Seizures, J. A. M. A. **122**: 1153-1156 (Aug. 21) 1943.

2. Abderhalden, E., and Hanslian, R.: Ueber das Verhalten von α-Pyrrolidoncarbonsäure im tierischen Organismus, Ztschr. f. physiol. Chem. **81**:228, 1912.

3. This basic food was Purina Chick Growena, prepared by the Ralston Purina Company, St. Louis. The food contains: dried buttermilk, meat scraps, soy bean meal, wheat germ, corn germ meal, wheat middlings, wheat bran, alfalfa meal, corn meal, salt beet pulp, cod liver oil and sardine oil. It was served in the form of a mash—2 parts of solid food to 1 part of water. Fresh water was available at all times through inverted siphon bottles.

4. Warner, L. H., and Warden, C. J.: The Development of a Standardized Animal Maze, Arch. Psychol., 1927, no. 92.

5. Jackson, T. A.: General Factors in Transfer of Training, Genetic Psychology Monographs, Worcester, Mass., Clark University Press, 1932, vol. 11, no. 1, p. 55.

during the early afternoon. The floors of the living cages were covered with sawdust, which was changed twice a week. After this three day period of adjustment, the feeding of the food supplements was started.

For the next three days each subgroup (5 rats) was fed in a special feeding cage. Each group received 75 Gm. of the basic food (Growena mash) containing the appropriate food supplement (basic food plus the selected amino acid). The control group was fed only the mash. The social incentive of group feeding overcame any preliminary reluctance on the part of any individual rat to eat food with a slightly different taste. Group feeding also served as a preliminary adjusting factor in relation to the ingestion of the food supplement. This period was followed by a two stage method of feeding. This method was adopted in order to insure an accurate administration of the food supplement and to maintain the normal health and growth of the rats.

The first stage consisted in feeding each rat individually. A dish containing 5 Gm.[6] of basic food, mixed with the required amount of the food supplement, was

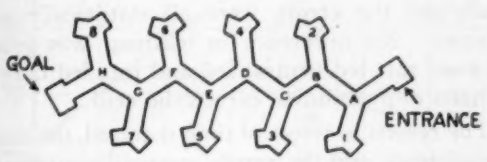

Fig. 1.—Pattern of the maze used in the present experiment. The letters represent the pathway units, and the numbers, the cul-de-sac units.

placed in a large dish. The control group received only the basic food. The daily dose given to each rat in the various groups is presented below:

dl-pyrrolidine carboxylic acid group...200 mg. of *dl*-pyrrolidine carboxylic acid

Neutralized pyrrolidine carboxylic acid group...200 mg. of *dl*-pyrrolidine carboxylic acid plus 130 mg. soduim bicarbonate.

Aminoacetic acid group...150 mg. of aminoacetic acid

Each rat was kept in his individual feeding cage until all this ration was eaten. This rarely required over twenty minutes. Since the floor of the individual feeding cage was bare, the experimenter could see easily whether or not all of the supplemented basic food had been eaten.

After the food supplement had been administered, the second stage of the feeding procedure occurred. Each subgroup (5 rats) was placed in a group feeding cage, where only the basic food was supplied. Large shallow saucers were used to insure sufficient feeding space for each rat in the group. When small deep dishes were used, one or two dominant rats frequently straddled the dish and kept the others away. A deep dish also encouraged the practice of carrying away morsels of food.

This procedure (two stage) was continued for eleven days, before maze training was started, as well as throughout the experiment. The rats were weighed daily on a gram weight-recording scale.

Testing Procedure.—The general procedure used in the experiment has been outlined in detail by Warden, Ross and Klein.[7] The procedure falls naturally into three phases: (1) the laboratory adjustment period, (2) the preliminary adjustment period and (3) the actual testing period.

The period of laboratory adjustment covered ten days, and the period of preliminary adjustment, four days. These stages, in which the rats became accustomed to diet, caging and handling conditions, coincided with the period of preliminary treatment, previously described. The preliminary treatment was carried out each day immediately before feeding. The entrance box, the goal box and a few unconnected pathway and cul-de-sac units were used. A small dish of basic food was placed in the entrance and goal boxes. Each rat was placed in the entrance box for three minutes and then in a goal box for three minutes. After this the animal was allowed to explore the disconnected cul-de-sacs and pathway units for four minutes. The order in and time at which the rats were tested were established at the beginning of this period and were maintained throughout the experiment. After the preliminary period of adjustment, the rat was given one trial (trial 0) of running through the connected maze. The usual data for the maze test were recorded for this trial but were not included in the results, since this trial was regarded as preliminary.

During the testing period, food was placed in the goal box only. The door of the entrance box was opened, the rat permitted to enter and the door closed behind him. The behavior (errors and time required) of the rat was recorded during the run through the maze. When the rat entered the goal compartment, the door was closed behind him, and a nibble of food was permitted. The time was taken by means of a stopwatch from the moment when the door of the entrance box was closed to the moment when the door of the goal box was closed.

After each rat finished this trial for the day, he was placed in his individual feeding cage. After feeding, as previously described, he was returned to his living cage, where no food but fresh water was available. The rats were thus starved approximately twenty-three hours prior to each trial.

The animals were subjected to the maze tests until they had reached a criterion of four out of five perfect trials. This criterion is as satisfactory as is a higher one of nine out of ten perfect trials, as shown by Warden.[8]

RESULTS

The results for each group of rats tested are shown in table 1. These results are stated in terms of trials necessary to reach the criterion, the total number of type A errors and the total time, expressed in seconds. The means and the standard derivations of these measures are presented in the table. The only errors considered

6. It was found in preliminary experiments that this amount of basic food (5 Gm.) served the purpose of providing sufficient dilution to mask the taste of the amino acid. It was also small enough to insure total ingestion in a short time by a rat starved approximately twenty-three hours.

7. Warden, C. J.; Ross, S., and Klein, G. S.: Laboratory Manual for Experimental Comparative Psychology, New York, Columbia University Press, 1943.

8. Warden, C. J.: A Comparison of Different Norms of Mastery in Animal Maze Learning, J. Comp. Psychol. **6**:155-179, 1926.

were the A type,[9] or forward-going entries into a cul-de-sac. The other types of error, backward-going entries into a cul-de-sac or a pathway unit, were not tabulated because they disappear early in maze learning.

It will be seen from an inspection of table 1 that the results fall into two discrete categories. The rats fed *dl*-pyrrolidine carboxylic acid and the rats fed neutralized *dl*-pyrrolidine carboxylic acid showed approximately the same order of means and standard derivations for each measure. On the other hand, the rats fed aminoacetic acid and the control rats showed the same general tendencies. In order to compare the differences in these measures for the groups, a test of the significance of the differences of the means of all

TABLE 1.—*Means for Performances of All Groups*

	dl-Pyrrolidine Carboxylic Acid Group		Amino-acetic Acid Group		Neutralized *dl*-Pyrrolidine Carboxylic Acid Group		Control Group	
	Mean	σ	Mean	σ	Mean	σ	Mean	σ
No. of trials....	5.2	3.6	17.2	7.3	4.0	2.3	13.6	9.6
Total number of errors.....	9.3	5.7	41.0	24.6	9.9	5.8	33.1	30.8
Total time, Sec.	180.3	148.1	657.9	455.4	175.1	157.4	553.3	535.3

TABLE 2.—*Significance of the Differences Between the Results for the Various Groups of Rats*

Group*	No. of Trials	No. of Errors	Time
Between P. C. A. group and aminoacetic acid group	6.70†	5.69†	16.08†
Between P. C. A. group and neutralized P. C. A. group.....	1.35	1.84	0.10
Between P. C. A. group and control group	3.82†	6.63†	3.11†
Between aminoacetic acid group and neutralized P. C. A. group.....	7.50†	5.38†	11.59†
Between aminoacetic acid group and control group	1.20	0.92	0.89
Between neutralized P. C. A. group and control group	4.42†	3.46†	3.06†

* P. C. A. in this table means *dl*-pyrrolidine carboxylic acid.
† The critical ratios thus designated are those which are equal to or greater than 3.

the groups was computed. The critical ratios were computed according to the method outlined by Garrett[10] (page 216); they are presented in table 2. The differences which are statistically significant (critical ratio equal to or greater than 3) are marked with a dagger.

It will be apparent from table 2 that there is a significant difference between the effects of ingestion of the *dl*-pyrrolidine carboxylic acid and the effects manifested by either the aminoacetic acid–fed rats or the control rats. This means that the difference observed in the mean number of trials required to learn the maze (5 trials for the rats fed *dl*-pyrrolidine carboxylic acid, as compared with 17 trials for the rats fed aminoacetic acid and 14 trials for the control rats) is statistically significant. On the other hand, the difference in the number of trials for the rats fed *dl*-pyrrolidine carboxylic acid and the number for the rats fed neutralized *dl*-pyrrolidine carboxylic acid is not significant and does not, in all probability, represent a real difference. From these results, it is clear that both groups of rats fed the *dl*-pyrrolidine carboxylic acid exhibited a quicker mastery of the maze than the aminoacetic acid–fed rats or the control rats. The results in terms of time required, the number of trials and the errors were all statistically significant. No difference in learning was found between rats fed neutralized and rats fed unneutralized *dl*-pyrrolidine carboxylic acid.

The results in terms of time required, the number of trials and the errors were all statistically significant. No difference in learning was found between rats fed neutralized and rats fed unneutralized *dl*-pyrrolidine carboxylic acid.

It is to be noted that the rats were fed *dl*-pyrrolidine carboxylic acid. This derivative of glutamic acid was effective in speeding up the learning of a simple maze. The specific physiologic action is still an unanswered question. This problem will be discussed further in the following section.

The *dl*-pyrrolidine carboxylic acid is derived from the racemic glutamic acid. The unnatural amino acids are not metabolized to any great extent in the animal body.[11] It is probable therefore that only the natural isomer of pyrrolidine carboxylic acid, the *l* form, is metabolized and that only this part of the compound administered accounts for the effects observed. This view is supported by the observation that *l*-pyrrolidine carboxylic acid, if fed to rabbits, is not excreted in the urine. It is possible that this substance is reconverted into natural glutamic acid. In this case the effect with *l*-pyrrolidine carboxylic acid may actually be due to that of *l*-glutamic acid. Experiment 2 is concerned with this problem.

It is unlikely that in the present experiment the ingestion of *dl*-pyrrolidine carboxylic acid made up for any dietary deficiency. It has been

9. Warden, C. J.; Jenkins, T. H., and Warner, L. H.: Comparative Psychology, New York, Ronald Press, 1935, vol. 1.

10. Garrett, H. E.: Statistics in Psychology and Education, New York, Longmans, Green & Co., 1940, p. 493.

11. Ratner, S.; Weissman, N., and Schoenheimer, R.: Paper presented at meeting of American Chemical Society, Division of Biological Chemistry, September 1941.

shown that inanition tends to make for speedier and more efficient maze learning in rats. It is apparent from figure 2, however, that inanition was not a factor here. There is no major difference in the growth curves for the different groups tested.

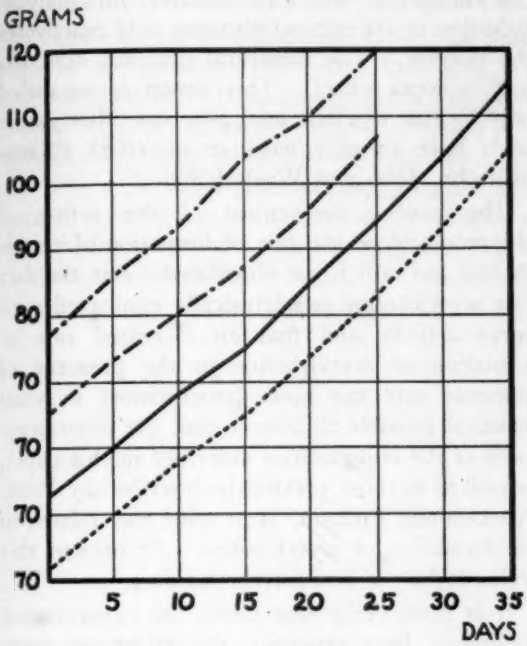

Fig. 2.—Weight curves for the various groups of rats in experiment 1. The values for the *dl*-pyrrolidine carboxylic acid group are indicated by a line of long and short dashes; the values for the rats fed neutralized *dl*-pyrrolidine carboxylic acid, by a line of dashes and dots; the values for rats fed aminoacetic acid, by a line of short dashes, and the values for the control rats, by a solid line.

EXPERIMENT 2

As indicated in the preceding section, this part of the study was concerned with the effect of ingestion of the naturally occurring *l*-glutamic acid on maze learning in the white rat.

TABLE 3.—*Means of the Performances of the Experimental (L-Glutamic Acid–Fed) and of the Control Group*

	Experimental Group		Control Group	
	Mean	σ	Mean	σ
Number of trials.....	8.9	2.7	12.1	3.7
Total number of A errors	8.5	5.2	36.5	15.5
Total time.....	287.7	196.7	666.1	382.0

The preliminary treatment and testing procedure were exactly the same as those employed in experiment 1. The experimental group consisted of 17 male albino rats and the control group of 9 rats. All of the rats (Sherman strain) were secured from Rockland Farms, Inc., New York. They were all of the same age as the rats of experiment 1 (6 weeks). The same maze pattern (fig. 1) as that employed in experiment 1 was used here.

RESULTS

The results for both groups are shown in table 3. The data are analyzed in terms of (1) the number of trials required to reach the criterion, (2) the total number of type A errors and (3) the total time, in seconds. The means and standard deviations for these measures are presented in the table.

It will be seen from an inspection of the table that the experimental group learned the maze in less time, required fewer trials and made fewer errors than the control group. The differences were statistically significant. The critical ratios were as follows: number of trials, 5.5; total number of type A errors, 4.6, and time, 5.3.

No statistically significant differences were found between the control group of experiment 2 and the control group of experiment 1.

It seems, also, of some value to compare the results for the rats fed *l*-glutamic acid with the results for the rats fed *dl*-pyrrolidine carboxylic acid in experiment 1. There was no difference of statistical significance between the performance of the two experimental groups. The following critical ratios were determined: number of trials, 0.6; total number of type A errors, 0.4, and time, 0.9.

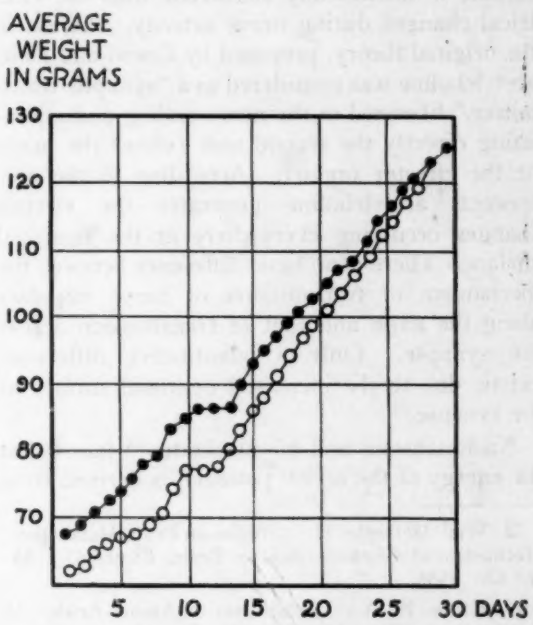

Fig. 3.—Weight curves for the groups of rats in experiment 2. The values for the experimental group, fed l-glutamic acid, are indicated by the solid circles, and the values for the control group, by the hollow circles.

In figure 3 will be found the weight curves for both groups. As in experiment 1, there was no significant difference between the growth curve for the control and that for the experimental group, and it does not seem likely that inanition played any part in the results.

COMMENT

A number of experiments have pointed to the fact that the natural, or *l*-glutamic acid has a particular relationship to cerebral metabolism. It has been reported by Weil-Malherbe [12] that *l*-glutamic acid is the only amino acid that is capable of maintaining the oxygen uptake of sliced brain tissue. Krebs [13] found an enzyme in brain tissue which synthesized glutamine from *l*-glutamic acid and ammonia. This synthesis is inhibited by the presence of the unnatural isomer. These experiments indicate a close relation between glutamic acid and the metabolism of brain tissue. Until recently there was, however, no indication how glutamic acid could possibly be connected with nerve function.

Recent investigations of Nachmansohn and his associates suggest that the release of acetylcholine is intrinsically connected with the electrical changes during nerve activity, whereas in the original theory, proposed by Loewi and Dale, acetylcholine was considered as a "synaptic transmitter," liberated at the nerve ending and stimulating directly the second unit (either the nerve or the effector organ). According to the new concept, acetylcholine generates the electric changes occurring everywhere at the neuronal surface. There is no basic difference between the mechanism of transmission of nerve impulses along the axon and that of transmission across the synapse. Only a quantitative difference exists, due to the increased neuronal surface at the synapse.[14]

Nachmansohn and his associates [15] found that the energy of the action potential is derived from energy-rich phosphate compounds. They concluded that these compounds yield the energy for the formation of acetylcholine, and, as a result of these observations, they isolated an enzyme from the brain which synthesizes acetylcholine (Nachmansohn and Machado [16]). This enzyme, choline acetylase, becomes inactive on dialysis. Addition of the natural glutamic acid reactivates the enzyme. The unnatural glutamic acid has only a weak effect. This action is paralleled only by that of citric acid, whereas other amino acids have either a weak or no effect (Nachmansohn, John and Waelsch [17]).

The precise mechanism of the action of glutamic acid on the rate of formation of acetylcholine has still to be elucidated. But the fact that acetylcholine is intrinsically connected with nerve activity and that an increased rate of formation of acetylcholine in the presence of glutamic acid has been demonstrated in vitro makes it possible to assume that the physiologic basis of the observations described in this paper, as well as of those previously described by Price, Waelsch and Putnam,[1] is in some way related to the formation of acetylcholine. At present this seems to be the best interpretation.

It is noteworthy that under the experimental conditions here reported, the effect on maze learning ability might be used as an indicator of metabolic conversions in the body. The experiments here reported suggest that *dl*-pyrrolidine carboxylic acid acts through the conversion of the *l*-pyrrolidine carboxylic acid into *l*-glutamic acid.

The results of the comparative feeding of aminoacetic acid indicate that a specific action of glutamic acid, and not the effect of an increased administration of nitrogenous compounds, is involved.

It is likely that there will be found other naturally occurring body constituents which may show the same effect as glutamic acid. Such substances may or may not be closely related to the metabolism of glutamic acid.[18]

12. Weil-Malherbe, H.: Studies on Brain Metabolism: Mechanism of Glutamic Acid in Brain, Biochem. J. **30**: 665-676, 1936.

13. Krebs, H. A.: Metabolism of Amino-Acids: II. Synthesis of Glutamine from Glutamic Acid and Ammonia, and the Enzymic Hydrolysis of Glutamine in Animal Tissues, Biochem. J. **29**:1951-1969, 1935.

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18. It has been recently shown by Harrell (Effect of Added Thiamin on Learning, Contribution to Education no. 877, Teachers College, New York, Columbia University Press, 1943, p. 55) that increased learning occurred with increased thiamine (vitamin B_1) intake in children. The superiority of the experimental group varied from 7 to 87 per cent for the eighteen measured activities.

SUMMARY AND CONCLUSIONS

1. Rats fed *dl*-pyrrolidine carboxylic acid and rats fed neutralized *dl*-pyrrolidine carboxylic acid made fewer errors, required fewer trials and learned the linear maze pattern in less time than either the aminoacetic acid–fed rats or the control rats. The differences were statistically significant.

2. The rats fed *dl*-pyrrolidine carboxylic acid required approximately the same time and the same number of trials and made about the same number of type A errors as did the rats fed neutralized *dl*-pyrrolidine carboxylic acid.

3. The rats fed *l*-glutamic acid learned the maze in fewer trials, with fewer errors and in a shorter time than did the control rats. The differences between the measures for the former and for the latter rats were all statistically significant.

From results 1 and 3, we conclude that *l*-pyrrolidine carboxylic acid and *l*-glutamic acid acted to enhance the learning of a simple maze.

This effect could not be related to inanition. The natural glutamic acid increases the rate of formation of acetylcholine in vitro.

Dr. Tracy J. Putnam made helpful suggestions in this work. Prof. C. J. Warden advised us in the development of the procedure and made available the animal laboratory of the department of psychology of Columbia University, where the experiments were performed.

Dr. H. Waelsch supplied the chemical compounds and the information given on them.

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EOSINOPHILIC GRANULOMA OF BONE PRESENTING NEUROLOGIC SIGNS AND SYMPTOMS

REPORT OF A CASE

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Eosinophilic granuloma is a newly recognized benign destructive lesion of bone. In 1940 Otani and Ehrlich [1] and Lichtenstein and Jaffe [2] described a solitary lesion of bone in which the medullary space was replaced by a granuloma packed with a multitude of eosinophils. Later, Farber [3] reported cases in which the lesions were multiple.

The cause is undetermined. Otani and Ehrlich expressed the belief that the disease follows local trauma, while Lichtenstein and Jaffe stated that an infectious agent was implicated, possibly a virus. Farber stated the opinion that eosinophilic granuloma is akin to Hand-Schüller-Christian disease and Letterer-Siwe disease.

Eosinophilic granuloma afflicts young persons of either sex and has a predilection for flat bones, although any bone may be affected. There are no symptoms of generalized illness—no fever, malaise, loss of weight or anemia. The classic signs of diabetes insipidus, exophthalmos, dwarfism and mental deterioration observed in cases of Hand-Schüller-Christian disease are absent. The patient consults his physician because of local symptoms associated with the growth of the tumor, or there may be no symptoms and the disease be accidentally discovered during the routine examination of roentgenograms. Local tenderness may be the only physical sign.

The roentgenogram reveals a localized, sharply punched-out area of rarefaction, with no surrounding reaction of bone. The lesions usually appear to be cystic or polycystic and show little or no tendency toward cortical expansion, although rupture through the cortex may occur. The roentgenographic appearance of the lesion is not unique and may be confused with that of many other diseases (table). A single lesion, or several lesions, may be encountered. The bones most frequently involved are the ribs, the vertebrae, the pelvis, the skull, the humerus and the femur.

Occasionally there is leukocytosis of mild degree, and rarely moderate eosinophilia is present. The levels of calcium, phosphorus, phosphatase, cholesterol and protein in the blood are normal. There is no change in the albumin-globulin ratio of the serum, and Bence-Jones protein is not present in the urine.

Eosinophilic granuloma may be confused with many diseases of diverse sorts. In the accompanying table these diseases and the differentiating features are listed. It is seen that in some cases only a biopsy will afford the final distinction.

The gross pathologic changes in the involved bone are roughening and irregularity of the cortex, with single, or more usually multiple, smooth-bordered perforations. The medulla is replaced by a brown or gray fibrous tissue, in the meshes of which lies a gray gelatinous material.

Histopathologic examination discloses a granulomatous lesion, composed of three main elements: (1) a reticulum of large, pale-staining cells with large, vesicular, oval or infolded nuclei, some of the cells having engulfed lipid material and occasional granules of fragmented eosinophils; (2) proliferation of fibroblasts, and (3) many eosinophils and eosinophilic myelocytes (fig. 1), which in some areas are so densely packed into masses that the eosin-stained section is bright red. Islands of necrosis may be scattered throughout. The bony trabeculae are destroyed and replaced by the granulomatous tissue. Rarely giant cells are present.

Cases with concomitant visceral lesions have been noted [4] but have not been fully described.

From the Neuropsychiatric Section, the Medical Service, the Laboratory Service and the Roentgenographic Section, Station Hospital, United States Army Air Base, Lincoln, Neb.

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Differential Diagnosis

Disease	Age Group	Roentgenographic Features	Clinical Features	Laboratory Observations
Eosinophilic granuloma	Children and young adults	Sharply defined, smooth, single or multiple cystlike areas of destruction, with no primary bone reaction; usually no expansion or erosion of cortex	No symptoms of a generalized illness; occasional mild local tenderness; most common in flat bones	Normal; slight eosinophilia (rare)
Hand-Schüller-Christian disease	Children	Picture usually indistinguishable from that of eosinophilic granuloma; defects in skull and pelvis sometimes present in large "geographic" patterns	Exophthalmos; diabetes insipidus; feeblemindedness	Anemia
Solitary bone cyst	Adolescents; young adults	Picture indistinguishable from that of solitary eosinophilic granuloma, although lesion is more common in extremities; cyst more apt to cause expansion of cortex	Shaft of a long bone usually involved; no symptoms; tendency to pathologic fracture	Normal
Enchondroma (single or multiple)	Children; young adults	Picture similar to that of solitary bone cyst	Most common in phalanges; may be multiple (congenital); no symptoms	Normal
Osteitis fibrosa cystica	Any age	Cystic changes similar to those in eosinophilic granuloma, but generalized bony rarefaction (decalcification) also present	Pathologic fractures; precocious puberty; pigmentation of skin; hyperparathyroidism	Increased serum calcium; lowered serum phosphorus; increased serum phosphatase
Gaucher's disease	Children	Expansion of shafts of long bones with thinning of cortex; sclerotic reaction of bone sometimes present	Familial; extreme splenomegaly without ascites; lesser degree of hepatomegaly and lymphadenopathy	Hypochromic anemia; leukopenia; thrombopenia (variable)
Multiple myeloma	Adults	Picture similar to that in eosinophilic granuloma, but defects usually smaller, more numerous and more uniform; changes in skull characteristic	General symptoms of malignant growth; local pain	Hyperproteinemia, with reversal of albumin-globulin ratio, 40%; Bence-Jones proteinuria, 40%; anemia, late appearance
Giant cell tumor	Children; young adults	Trabeculated polycystic defect at ends of long bones, causing expansion of cortex	Involvement of ends of long bones or epulis of jaw; no symptoms; tendency to fracture; lesion rarely malignant	Normal
Osteogenic sarcoma	Children; young adults	Irregular destruction of bone, combined with irregular formation of new bone	Involvement of ends of shafts of long bones and pelvis; pain followed by appearance of tumor; lesion usually single; fixation of soft parts	Increase of serum phosphatase (variable)
Ewing's tumor	Children; young adults	Irregular destruction of medullary bone, with subperiosteal formation of new bone; "onion skin" effect sometimes present	Involvement of long bones, pelvis and os calcis; trauma followed by intermittent pain and fever, followed by appearance of tumor; spread to other bones, including skull; temporary response to rentgenotherapy	Low blood calcium (occasional)
Osteomyelitis	Any age	Irregular destruction and proliferation of bone; formation of sequestrum and involucrum	Frequent occurrence in long bones; fever and malaise; local tenderness	Leukocytosis
Tuberculosis	Children; young adults	Irregular destruction of ends of long bones and vertebrae; involvement of joints; ribs rarely affected	Involvement of joints; muscle spasm and atrophy of adjacent soft structures; characteristic deformities; loss of weight and low grade fever when present	Positive tuberculin reaction; aspiration of material and injection into guinea pig; anemia (variable)
Syphilis	Any age	Proliferation usually overshadowing destruction of bone; solitary gumma may resemble solitary eosinophilic granuloma	History of congenital or acquired syphilis; symmetric osteochondritis with congenital and gummatous periostitis and osteitis with late acquired syphilis	Positive serologic reactions
Neurofibromatosis	Older adults	Defects similar to those in eosinophilic granuloma, but usually near ends of long bones; lesion may rupture cortex	(1) Nodular tumors along peripheral and deep nerve trunks, with café au lait spots; (2) single or multiple lesions of spinal cord, with erosion of laminas and symptoms of extradural pressure, (3) acoustic nerve tumor, leading to signs of tumor of posterior fossa	Normal
Gout	Adult males	Small, sharply circumscribed, rounded areas of rarefaction, usually occurring in feet or hands	Recurrent acute, painful arthritis; frequent occurrence in small bones of extremities, especially great toes; association with ingestion of beer, wine and purine foods; tophi	Increased uric acid content of serum (variable)

The original treatment was excision of the diseased area.[5] Later, Farber found that roentgenotherapy arrested the progress of the disease and caused the disappearance of the lesions. A total dose of 1,500 roentgens is recommended.[4] New lesions may appear several years after an apparent cure; therefore the patient should continue to have periodic examinations.

The prognosis for individual bone lesions is good. However, Farber[4] has seen cases with visceral lesions which were fatal.

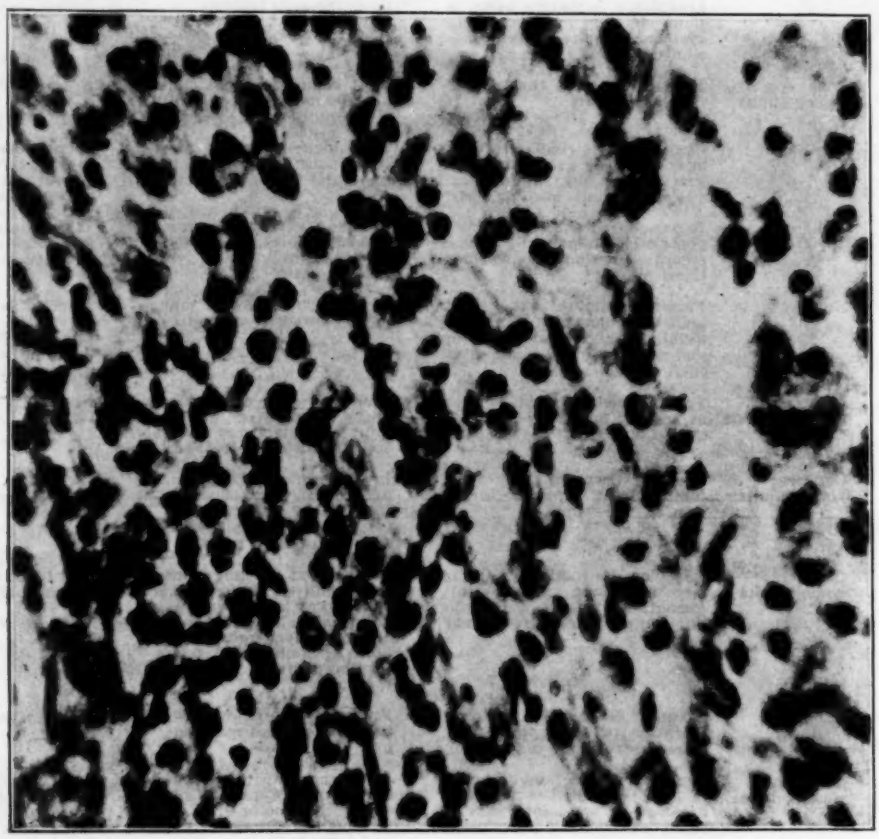


Fig. 1.—Photomicrograph of a biopsy specimen from the rib, showing large macrophages, eosinophils, eosinophilic myelocytes and occasional fibroblasts. High power magnification.

REPORT OF CASE

History.—C. L., a soldier aged 21, was first admitted to the neurologic section on Nov. 19, 1942. That morning, when he awoke, he noticed that his face was paralyzed on the left side. There was no difficulty in ability to taste, but he complained that he could not close his left eye completely.

Nothing in the past history threw any light on his disorder except for an infection of the left ear in childhood. The ear had discharged purulent material at the time, but for the past decade and a half there had been no further trouble. There was no headache, giddiness or vomiting. The right ear drum appeared normal. Examination of the mouth showed absence of many teeth, as the result of previous extractions. The pupils were equal, and the right pupil was slightly irregular. The left tympanic membrane was thickened, scarred and retracted, but showed no signs of recent inflammation. Neurologic examination showed an entirely normal status except for the cranial nerves. The face was completely paralyzed on the left side and was asymmetric when at rest, with exaggeration of the asymmetry on voluntary and mimetic movement. There was lagophthalmos, and the tears ran down the cheek instead of into the lacrimal duct. The levator and the Negro signs were present. The tip of the nose was drawn toward the sound side of the face, with flattening of the nasolabial fold on the affected side. The mouth was also drawn toward the sound side, and there was inability to whistle. Articulation of the labial consonants was impaired. There was no loss of pressure pain sense over the face or involvement of taste sense in the anterior part of the tongue. There was mild hyperacusis. By December 4 the palsy had entirely cleared, and the patient was discharged, with orders to report for observation in the outpatient department.

He was readmitted to the otorhinolaryngologic service on March 31, 1943, with complaints of vertigo, falling to the right and pain and tenderness over the first thoracic vertebra. An etiologic diagnosis was not made. By April 6 he had improved greatly and was discharged with a diagnosis of Ménière's syndrome.

However, during the next week his symptoms became acute, and he returned to the neurologic outpatient

5. Otani and Ehrlich.[1] Lichtenstein and Jaffe.[2]

department. He complained of intense vertigo with falling to the right, accompanied by nausea. Between the attacks of vertigo, which came on daily, he had a feeling of giddiness. He complained of a buzzing noise in his left ear, and for two days he had experienced a feeling of numbness and burning in that ear.

Physical and Neurologic Examination.—There was tenderness over the first dorsal vertebra. The abnormalities noted in the neurologic examination were confined to the cranial nerves. The pupils were equal, the right being slightly irregular and flattened at 6 o'clock, and, as noted in the previous examination, reacted well to light and in convergence, both directly and consensually. The external ocular movements were normal. There were coarse horizontal nystagmoid jerks on extreme lateral gaze, especially to the right, which was the direction of the quick phase. No facial palsy was now apparent. There was slight deafness of the left ear. The patient could not hear the C 128 tuning fork when it was adjusted for the key of B. He heard A slightly and G better, and his hearing increased as deeper tones were approached. Audiometric readings confirmed these observations. Hearing in the right ear was normal. Bone conduction was greater than air conduction in the left ear in the Rinne and Schwabach tests. In the Weber test the sound was referred only slightly to the left. The left tympanic membrane showed scarring and retraction, as noted in the previous examination. There were hypalgesia and hypesthesia over the left auricle in the distribution of the facial nerve (Wrisberg). The other cranial nerves were normal. The patient was transferred to the medical service.

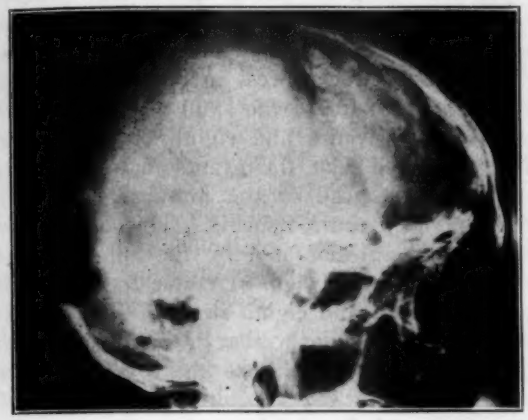


Fig. 2.—Roentgenogram of the skull, showing areas of rarefaction of the left temporal bone.

Roentgenographic Studies.—Roentgenograms were made of all the bony structures. Destructive lesions were noted in the left temporal bone (fig. 2), the mandible, the first and second thoracic vertebrae, the seventh cervical vertebra, the first, second, third and fifth ribs on the left side, the first and third ribs on the right side, the right femur and the transverse process of the fifth lumbar vertebra. There was also questionable involvement of several lower dorsal and upper lumbar vertebral bodies. The lesions generally were sharply punched-out, solitary or confluent polycystic defects with smooth borders. There was no appreciable tendency toward expansion of the cortex and no significant reaction of the bone.

Roentgenograms of the skull disclosed a lesion in the left temporal bone, which consisted of a polycystic defect involving the posterior squamous portion and extending into the petrous portion to involve the region of the internal auditory meatus (fig. 2). The remainder of the mastoid appeared underdeveloped and sclerotic, the condition apparently representing the end result of disease in childhood. The spinal lesions of clinical significance were those affecting the bodies and processes of the first and second dorsal vertebrae, associated with kyphosis and sharply localized scoliosis. The most extensive lesions of the thoracic cage were those of the fifth rib, from which the biopsy specimen was taken. There was a pathologic fracture of the second rib on the left side. The pelvis and the bones of the extremities were uninvolved except for a polycystic defect in the distal end of the left femur.

Laboratory Data.—Routine examination of the urine revealed nothing significant. No Bence-Jones protein was present. The red blood cell count was 4,400,000; the hemoglobin measured 13 Gm. (14.5 Gm. is equivalent to 100 per cent), and the white blood cell count was 9,000, with 62 per cent neutrophils and 1 per cent eosinophils. The erythrocytic sedimentation rate was 17 mm. per hour (normal, 10 mm. per hour). The protein of the serum was 6.6 Gm., the albumin 3.9 Gm. and the globulin 2.7 Gm. per hundred cubic centimeters. The calcium of the blood measured 10.4 mg., the phosphorus 4 mg., and the phosphatase 2.8 Bodansky units per hundred cubic centimeters; the cholesterol of the serum was 160 mg. per hundred cubic centimeters. Lumbar puncture revealed that the dynamics, the cell content, the total amount of protein, the Pandy reaction, the colloidal gold curve and the Wassermann reaction were normal.

Fig. 3.—Roentgenogram of the skull, showing filling in of lesions in the left temporal bone after roentgenotherapy.

Biopsy.—Three biopsies were performed. Two specimens were taken respectively from the lesions on the right and the left side of the mandible, and one was obtained from the involved portion of the left fifth rib. In each specimen there were destruction of bone and replacement with a gray granulation tissue, in the meshes of which was a gray gelatinous material. The lesion on the left side of the mandible had destroyed the wall of the mandibular canal and surrounded, but not attacked, the inferior alveolar nerve. Histologic

examination of all three specimens showed the typical changes of eosinophilic granuloma (fig. 1).

Treatment.—The patient was given three courses of roentgenotherapy. At the time of writing, four months after therapy was begun, and ten months after his initial admission, he is completely free from all neurologic signs and symptoms. Roentgenograms taken at this time showed partial recalcification of some of the bony defects (fig. 3). No new lesions appeared, and the patient's general condition was excellent.

COMMENT

No case of eosinophilic granuloma with neurologic symptoms and signs has previously been reported. The present case is unique in that the presenting complaints were referable to the nervous system. But inasmuch as the disease has only recently been recognized, time will undoubtedly result in the observation of similar cases. The early recognition of the disease is important because of the favorable response to roentgenotherapy.

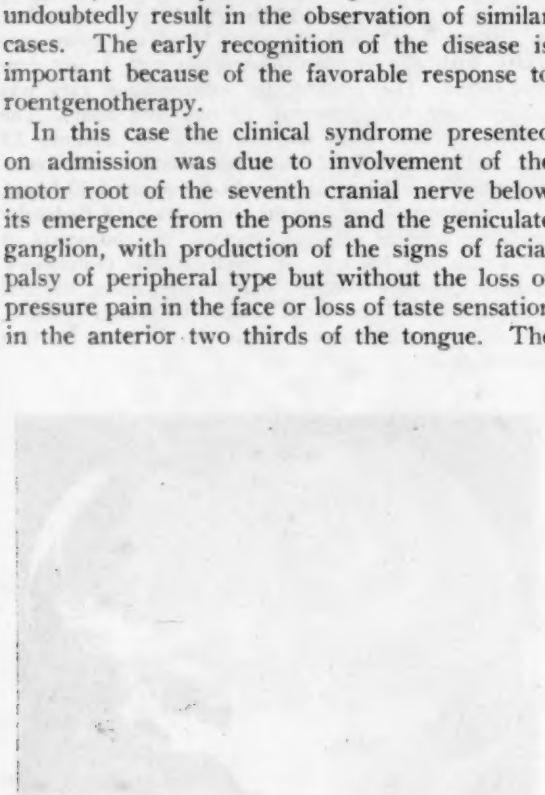
In this case the clinical syndrome presented on admission was due to involvement of the motor root of the seventh cranial nerve below its emergence from the pons and the geniculate ganglion, with production of the signs of facial palsy of peripheral type but without the loss of pressure pain in the face or loss of taste sensation in the anterior two thirds of the tongue. The auditory nerve escaped, with resulting hyperacusis due to paralysis of the stapedius muscle.

Subsequently, with spread of the basal intracranial disease, general symptoms of headache, giddiness and vomiting appeared. Then the eighth nerve was involved, with resulting deafness, tinnitus, vertigo, nausea, vomiting and nystagmoid jerks. Finally, the process spread to involve the geniculate ganglion, with production of deep-seated pain in the ear and the region of the mastoid.

The destructive process in the skull involved the wall and floor of the skull in the region of exit of the seventh and eighth cranial nerves. It is assumed that the granulomatous process destroyed the wall of the foramen, with production of pressure neuritis. This assumption is partially substantiated by the subsidence of the symptoms and signs referable to the lesions of the seventh and eighth nerves. The process was evidently similar to that in the jaw, in which the mandibular canal was destroyed, but the inferior alveolar nerve, although surrounded, was not invaded.

SUMMARY

In a case of eosinophilic granuloma of bone reported here the presenting signs and symptoms were referable to the nervous system.



ANDROGEN THERAPY FOR INVOLUTIONAL MELANCHOLIA

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Elsewhere one of us (L. D.)[1] has presented evidence to show that a psychosis due to estrogen deficiency exists and responds promptly to appropriate therapy. To prove the existence of a psychosis due to androgen deficiency is more difficult because of the vagueness of the diagnostic criteria. The evidence for the existence of such a psychosis will be reviewed in the present paper, and the results of therapy in new cases will be described.

For some years, numerous psychiatrists and endocrinologists have been interested in the treatment of involutional melancholia in the male with androgens. Because of the comparative rarity of the disorder and the difficulty of the diagnosis, it is not reasonable to expect a single hospital to contain a large number of patients suitable for study. It is only when the results of many investigations are pooled that figures for statistical treatment can be collected.

In the present paper are summarized the reports which have appeared in the more readily accessible journals in English during the seven and one-half years ending June 30, 1943. During this period the treatment with androgens of 83 patients suffering from involutional melancholia was reported. The results are shown in table 1.

Inspection of the table reveals that the experience of individual investigators varied from the most favorable results to failure. Pooling of the results shows that the percentage of patients who recovered or improved notably during the therapy did not increase as the dose of androgen was increased and that for the whole series studied the incidence of favorable responses was only 37 per cent.

Such a percentage is of course lower than can be expected from convulsive therapy and is not higher than the spontaneous rate of improvement reported by the United States Bureau of the Census.[2] It should be remembered, however, that the patients who improve under androgen therapy do so during the brief period of treatment, while those who improve spontaneously do so at any time. Androgen therapy may, then, at least shorten the course of the illness in certain patients, with important economic advantage to the patient and to the hospital.

The reports of individual cases indicate that patients who benefited from androgen therapy improved dramatically, as though they were receiving appropriate, or even specific, therapy. This is strikingly illustrated by patients who relapsed after the treatment was discontinued and who improved again with a second course of therapy.[3] Patients who had shown no improvement after long periods of treatment in a hospital or whose condition had not changed when they were given placebos[4] might be entirely well after a small number of injections of androgen. The implications of such results should not be overlooked, even though the majority of men so treated do not improve.

The impression that treated patients are more likely to recover quickly than untreated patients may be given quantitative expression, in accordance with the following analysis:

Of the 83 men referred to in the table, 18 recovered during the period of treatment, and 16 are known to have recovered in three months or less. Thus, at least 19 per cent of the treated patients recovered in three months or less. This percentage should be compared with the incidence of spontaneous recovery for untreated

From the Milwaukee County Hospital for Mental Diseases.

Presented at a meeting of the Milwaukee Neuro-Psychiatric Society, Oct. 28, 1943.

1. Danziger, L.: Specific Treatment of Psychosis Due to Estrogen Deficiency, to be published.

2. Mental Patients in State Hospitals, United States Department of Commerce, Bureau of Census, 1931 and 1932; Patients in Hospitals for Mental Disease, ibid., 1933; Patients in Mental Institutions, ibid., 1934, 1935 and 1936.

3. (*a*) Guirdham, A.: Treatment of Mental Disorders with Male Sex Hormone, Brit. M. J. **1**:10, 1940. (*b*) Werner, A. A.: The Male Climacteric, J. A. M. A. **112**:1441 (April 15) 1939. (*c*) Zeifert, M.: Massive Dose Testosterone Therapy in Male Involutional Melancholia, Psychiatric Quart. **16**:319, 1942.

4. Danziger, L., and Blank, H. R.: Androgen Therapy of Agitated Depressions in the Male, M. Ann. District of Columbia **11**:181, 1942.

patients as given by the United States Bureau of the Census.[2] In this survey the published reports for the five years 1931 to 1935 were selected because in this period the prognosis was not affected by shock therapy or, to any appreciable extent, by androgen therapy. In these five years, in all the state hospitals of the United States, 470 men with a psychosis diagnosed as involutional melancholia were admitted each year, and 264 were discharged. Of this number, 183 per thousand men admitted with the same psychosis were discharged per year as recovered. (The figures given are the means for the five year period. The extremes are 431 and 542 admissions, 235 and 315 discharges and 162 to 213 recoveries.)

Of 1,000 men admitted with involutional melancholia, therefore, 183 can be expected to be discharged eventually as recovered.

For the middle year of the period, 1933, the number of recoveries was reported as a function of the duration of the last period of hospitalization. In this year, of the men discharged as recovered, 26 had been in the hospital for three months or less. From these figures it is easy to see that of 1,000 men admitted because of involutional melancholia, 55 will be discharged as recovered in three months or less. The expectation of spontaneous recovery in three months is therefore 5.5 per cent.

Of the treated group in our series, 19 per cent recovered in three months or less. The expectation of recovery under treatment is apparently over three times the expectation of spontaneous recovery. By the Pearson chi square test, the odds in favor of the significance of the difference of the two percentages are more than 16,000 to 1.

Since the patients in the treated group were not all treated during the first three months of hospitalization, the odds are really still more favorable. Thus, while at first glance the results shown in table 1 are not good, they prove on closer analysis to be better than those for control patients. However, they are not as good as could be obtained if the therapy were specific. The failure of the incidence of improvement to increase as the dose is increased also argues against the specificity of the treatment. It is quite possible, however, that the treated group of patients was not homogeneous with respect to the disease. Such heterogeneity would explain the low incidence of improvement.

In the study of estrogen therapy for psychotic women [1] evidence was presented to show that the therapy is specific for patients whose psychosis may reasonably be ascribed to estrogen deficiency. The striking phenomena of the menopause are, of course, of great value in the selection of women suitable for treatment. The absence of such phenomena in men makes the intelligent selection of male patients difficult. Evidence of androgen deficiency may be obtained in various ways, but these procedures do not indicate when the deficiency developed or whether the onset of the deficiency had any close temporal relation to the onset of the psychosis.

TABLE 1.—*Data on Androgen Treatment of Eighty-Three Men with Involutional Melancholia Whose Cases Are Reported in the Literature*

Authors	Weekly Dose of Testosterone Propionate	Number of Patients	Patients Recovered or Greatly Improved	
			Number	Percentage
Palmer, H. D.; Hastings, D. W., and Sherman, S. H.: Am. J. Psychiat. **97**: 1067, 1941	40 mg. or less	10	2	
Barahal, H. S.: Psychiatric Quart. **12**: 743, 1938		5	0	
Guirdham [3a]		4*	4	
Pardoll, D. H., and Belinson, L.: J. Clin. Endocrinol. **1**: 138, 1941		11	1	
Thomas, H. B., and Hill, R. T.: Endocrinology **26**: 953, 1940		2	2	
Werner [3b]		2	2	
	Totals for group	34	11	33
Kerman, E. F.: Arch. Neurol. & Psychiat. **49**: 306 (Feb.) 1943	41 to 200 mg.	12	1	
Davidoff, E., and Goodstone, G. L.: Arch. Neurol. & Psychiat. **48**: 811 (Nov.) 1942		20	5	
Lamar, C. P.: J. Florida M. A. **26**: 398, 1940		4	4	
Miller, N. E.; Hubert, G., and Hamilton, J. B.: Proc. Soc. Exper. Biol. & Med. **38**: 538, 1938		2	2	
Werner, A. A.: North End. Clin. Quart. **2**: 18, 1941		1	1	
Danziger and Blank [4]		5	3	
	Totals for group	44	16	36
Zelfert [3c]	Over 200 mg.	5	4	
	Totals for group	5	4	80
	Grand totals	83	31	37

* Some patients received androsterone benzoate.

Occasionally a history of castration, bilateral orchitis, hot flashes, anginoid attacks or symptoms of prostatic hypertrophy immediately preceding the onset of the psychosis is obtained. In such cases the diagnosis of psychosis due to androgen deficiency is more secure. In the majority of cases, however, it is at present necessary to be satisfied with the clinical signs and symptoms of involutional melancholia.

With the difficulties of diagnosis in mind, we selected 9 patients for androgen therapy. Each patient was given a preliminary course of injections of sterile water three times a week, followed by a course of intramuscular injections of testosterone propionate. Injections of the placebo were given for at least one month. No patient improved under the placebo treatment. Testosterone propionate [5] was given in 25 mg. doses three times a week. One patient, who failed to improve on this regimen after six weeks of androgen treatment, was given the testosterone daily for four weeks; he failed to improve. Of the 9 patients, 5 recovered and 1 other showed decided improvement. It is possible that of the 3 patients who failed to improve the psychosis of 1 was due to chronic alcoholism and 1 had manic-depressive psychosis. The individual histories follow.

TABLE 2.—*Behavior Chart of a Man with Involutional Melancholia During Treatment with Testosterone*

March 1943.....	1	2	3	4	5	6	7	8*	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Talking.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+
Industrious.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	±	±	±	±	±	±	±	±	±	±
Cheerful.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	±	±	+	+	+	+	+	+	+	+	+	+
Smiling; laughing ..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	±	±	+	+	+	+	+	+	+	+	+	+
Played games.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+
Read.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+
Quiet.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uninterested.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	..	..	..	..	..	..	..	..	..	..	..	..
Brooding.....	+	+	+	+	+	+	+	+	+	+	+	+	±	±	±	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Sad.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	±	±	..	..	..	..	..	..	..	..	..	..	..	..	..
Anxious.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	±	±	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Apprehensive.....	+	+	+	+	+	+	+	+	+	+	+	+	±	±	±	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Refused to speak..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	..	..	..	..	..	..	..	..	..	..	..	..
Motionless.....	+	+	+	+	+	+	+	+	+	±	±	±	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Exercised.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	..	+	+	+	+	+	+	..	+	+	+
Saw visitors.....	..	+	..	..	..	..	+	..	..	..	..	..	+	..	..	..	..	..	..	..	+	..	..	..	..	..	..	+	..	..	..
Bathed.....	+	..	..	+	..	..	..	+	..	..	+	..	..	..	+	..	..	+	..	..	..	+	..	..	+	..	..	..	+	..	..
Appetite good.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	+	+	+	+	+	+	+	+	+	+	+	+
Appetite fair.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	..	+	+	..	..	..	..	..	..	..	..	..	..	..	..

* Treatment with testosterone propionate was begun on this date.

REPORT OF CASES

CASE 1.—O. S. was born in 1882; his birth and early development were normal. He completed the fourth grade in a rural school and spent much of his early life on a farm. Later he worked as an unskilled laborer. Although he was always considered seclusive and somewhat odd, he adjusted satisfactorily until the present illness. He never married.

In January 1942 he complained of feeling old and said his death could be expected soon. He remained at home in bed, appeared at times to be confused and preoccupied and said he had a "funny feeling in his mind." He was admitted to the Milwaukee County Hospital for Mental Diseases on Feb. 10, 1942.

On admission he was disoriented and apparently depressed. Much of the time he was mute, and when he spoke his remarks were incoherent. Physical examination showed moderate arteriosclerosis and some ataxia. The results of laboratory studies were noncontributory.

The patient was paroled, as slightly improved, on Nov. 4, 1942 and was readmitted to the hospital on Feb. 5, 1943. His condition was essentially the same as on the first admission. Injections of a placebo were started on February 8, and testosterone therapy was begun a month later. After the fourth injection of testosterone he became less apprehensive and depressed, and after the sixth injection he began to speak freely. After the seventh injection he appeared entirely normal. Treatment was continued until April 14. On April 13 he was visited by his sister, who said he was as well as he had been before the onset of the psychosis. He was paroled on May 30. His behavior chart (table 2) illustrates the prompt and dramatic improvement often seen with androgen therapy.

CASE 2.—C. C. was born in 1882. The family and past histories were noncontributory. In February 1939 the patient complained of insomnia, anorexia, fear of blindness and death and frequent sensations of chilliness. He expressed the belief that something kept him from eating and that various unidentified persons were against him. He became agitated and depressed and was therefore admitted to the Hospital for Mental Diseases on June 10, 1939.

On admission he was agitated and depressed. The sensorium was clear. Physical examination revealed minimal arteriosclerosis. Laboratory studies revealed nothing abnormal. He improved slightly and was paroled on April 5, 1940. He was readmitted to the hospital on Oct. 1, 1940. He was given metrazol therapy, with which he showed temporary improvement. In a convulsion, however, he sustained a fracture of the neck of the femur, which failed to unite.

In 1943, after four years of nearly continuous hospitalization, the patient was still depressed and agitated.

5. The testosterone propionate used in this study was furnished by Dr. Edward Henderson, Schering Corporation, Bloomfield, N. J.

Injections of a placebo were started on February 10, and testosterone therapy was begun a month later. After the fourth injection of the androgen he spoke for the first time in several months. Thereafter he rapidly became less depressed, took an interest in ward activities and joked with the nurses. After the twelfth injection he appeared to be free of all psychotic symptoms. Treatment was continued until May 13, when he was considered by the staff to be ready for parole, but his family were unable to take care of him because the fractured bone did not unite.

CASE 3.—J. F. was born in 1876. The family history was noncontributory. The patient was considered somewhat seclusive but not otherwise abnormal. He never married. His health had been good until the present illness.

In May 1935 he complained of fear of death, said a mob was waiting outside the house to kill him and became depressed and agitated. Because of suicidal preoccupations he was admitted to the Hospital for Mental Diseases on Sept. 7, 1935. On admission he was agitated, fearful and depressed. He insisted that he had syphilis and that he must therefore kill himself. The sensorium was clear. Physical examination and laboratory studies revealed nothing of interest.

In the hospital there was slight improvement. The patient became able to do light work in the ward, but he continued to be anxious, depressed and for the most part mute. Injections of a placebo were started on Feb. 10, 1943, and testosterone therapy was begun a month later. After the fifth injection of the androgen he became less anxious and thereafter gradually improved. After the fifteenth injection he was cheerful and had apparently recovered from his depression. Treatment was continued until May 13. Although he recovered from his psychosis, he is so thoroughly institutionalized that as yet it has been impossible to arrange for his parole.

CASE 4.—W. L. was born in 1886. His father had a mental illness somewhat similar to that of the patient; otherwise the family history was noncontributory. The patient's early life was uneventful. He was a successful architect and was happily married. He had been well until the present illness. There was a questionable history of chronic alcoholism.

About 1937 the belief gradually developed that his drinking water was contaminated and that his food was poisoned. He thought gas escaped in his house and that his co-workers were jealous of his success. He became increasingly quiet and morose and was admitted to the Hospital for Mental Diseases on June 21, 1939.

On admission he complained that his bowels had not moved for two years and that his intestine was closed. He was depressed, agitated and preoccupied. Physical examination and laboratory studies revealed nothing of interest. There was no change in his condition during the next four years. After a preliminary course of injections of a placebo, he was given injections of testosterone propionate three times a week for six weeks and then daily for four weeks, without improvement.

CASE 5.—H. S. was born in 1882. A paternal cousin was believed to have had a mental illness; otherwise the family history was noncontributory. The patient completed the eighth grade and thereafter worked successfully as a salesman. He was happily married and had been well until the present illness. He was jovial and outgoing, with many friends and wide interests.

In 1933 the patient became depressed and expressed the belief that he was involved in the Lindbergh kidnaping. He claimed the police wished to question him. He stopped work and thereafter was supported by his wife. He was not hospitalized, and in 1936 he showed slight improvement. He was able to do some work, but not to support his wife. In 1939 he became much worse and spent most of the next year in bed. He complained of numbness in the left arm and of abdominal distress. In June 1940 the family physician made a diagnosis of carcinoma of the stomach. At about this time the patient said he felt compelled to kill some one. He was therefore admitted to the Hospital for Mental Diseases on June 24, 1940.

On admission he was depressed and agitated. He spoke of his connection with the Lindbergh case and accused himself of other crimes. He ate poorly and for a time was fed by tube. No somatic delusions were elicited. The sensorium was clear. Physical examination revealed arteriosclerosis. Laboratory studies, including roentgenographic examination of the gastrointestinal tract, revealed nothing of interest.

After nearly three years of continuous hospitalization the patient had not improved. He took no food except the mixture to be fed by tube; this he drank. After a preliminary course of injections of a placebo he was given testosterone propionate three times a week for fourteen weeks, without improvement.

CASE 6.—L. B. was born in 1889. The family history was noncontributory. The patient completed the eighth grade and thereafter worked steadily as an unskilled laborer. He was happily married. He was a quiet, conscientious worker, with wide interests and many friends. He had been well until the present illness.

On Jan. 16, 1943 he injured his back while at work. Three months later he received a letter relating to workmen's compensation. He had difficulty in understanding it, and soon after he expressed the belief that his co-workers had turned against him. He became depressed and agitated, slept poorly and stated the conviction that his family was to be turned out by the landlord. He was therefore admitted to the Hospital for Mental Diseases on May 21.

On admission he was suspicious, sullen, agitated and depressed. No somatic delusions were elicited. The sensorium was intact. Physical examination and laboratory studies revealed nothing of interest.

After a preliminary course of injections of a placebo, testosterone propionate was given three times a week for two months, with no improvement. Later the patient showed striking improvement with electric shock therapy.

CASE 7.—R. P. was born in 1889. The family history was noncontributory. The patient completed the fourth grade at the age of 14 years. Thereafter he worked steadily as a mechanic and molder. He never married. He was considered asocial but not otherwise abnormal.

In July 1935 he complained of the excessive heat and rapidly became depressed, agitated and suicidal. He spoke only in whispers and usually refused to answer questions. He attempted suicide early in August 1935 and was admitted to the Hospital for Mental Diseases on August 17.

On admission he was greatly depressed, agitated and preoccupied. On one occasion he said he heard voices coming to him through the air. No somatic delusions were elicited. The sensorium was consistent with the patient's education. Physical examination and laboratory studies revealed nothing of interest.

During the next eight years the patient was depressed, agitated and usually mute. Occasionally he did a little work in the ward, but he never showed interest in his surroundings or in the other patients. A course of injections of a placebo was started on Feb. 10, 1943, and testosterone propionate therapy was begun a month

later. After the sixth injection of the androgen he began to improve. He gradually became cheerful, spoke freely, ate and slept well and worked industriously every day. Treatment was discontinued on June 7. Improvement was considered excellent.

CASE 8.—W. D. was born in 1885. The family history was noncontributory. The patient completed the sixth grade and thereafter worked steadily as a shipping clerk and unskilled laborer. He was happily married and had 1 child. He was described as sensitive, shy, conscientious and worrisome, with little social poise and a poor opinion of his own ability. He had been well until the present illness.

In the spring of 1942 the patient gradually became depressed and said his work was unsatisfactory. In April 1943 he expressed the belief that the factory police were watching him, and he became more depressed and agitated. He had crying spells and made one attempt at suicide. He was therefore admitted to the Hospital for Mental Diseases on May 7.

On admission he was agitated and depressed. He said he had been having hot flashes for several months, but he was unable to give the date of their onset. The sensorium was consistent with the patient's education. Physical examination and laboratory studies revealed nothing of interest. He failed to improve in the hospital, and injections of a placebo were started on June 4. Testosterone propionate was substituted for the placebo on July 5. After the ninth injection of the androgen the patient became much less depressed and agitated, had a good appetite and slept well. After the fifteenth injection he appeared to be entirely well. Treatment was discontinued on September 22, and the patient was paroled as recovered on September 30.

CASE 9.—F. K. was born in 1888. One sister had a postpartum mental illness, from which she recovered without hospitalization. The patient completed the sixth grade and thereafter worked steadily as a semiskilled laborer. He was happily married and had 1 child. He had been well until the present illness. He was described as quiet, interested in hobbies, which he pursued at home, and devoted to his family. He had few friends.

In August 1942 the patient was injured at work. He was sent home, where he rapidly became greatly depressed. He was motionless for long periods, refused to bathe, slept in his clothes and said his bowels were stopped up. At times he had visual hallucinations and expressed the belief that a priest wished to harm him. He was admitted to the Hospital for Mental Diseases on July 23, 1943.

On admission he was agitated, depressed, apprehensive and indecisive. He ate and slept poorly, concentrated with difficulty, picked and rubbed at his skin and expressed suicidal preoccupations. The sensorium was consistent with his education. Physical examination and laboratory studies revealed nothing of interest.

The patient failed to improve with a course of injections of a placebo, begun July 30, and on September 22 injections of testosterone propionate were started. He began to improve after the first injection of the androgen. He became less depressed, spoke freely and began to take an interest in activities in the ward. His sleep and appetite improved, and the indecisiveness disappeared. Treatment was discontinued on October 29, at which time the patient was considered recovered.

SUMMARY

A review of the literature in English on androgen therapy of involutional melancholia in the male indicates that the incidence of prompt recovery for the treated patients is significantly higher than the incidence of prompt spontaneous recovery for control patients.

Of 9 new patients treated with androgen, 5 recovered and 1 improved notably.

Box A.
Milwaukee County Hospital for Mental Diseases.

SPECIFIC TREATMENT OF PSYCHOSIS DUE TO ESTROGEN DEFICIENCY

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In an earlier report,[1] I reviewed the literature in English on the estrogen therapy of patients with agitated depressions which had been published up to Dec. 31, 1940. A number of opinions expressed in that study and implied by the figures presented can now be reconsidered in the light of information since collected.

In the previous study, of 164 patients treated with estrogens over a sufficient time, only 79 (48 per cent) recovered or showed notable improvement during the period of therapy. The percentage of patients successfully treated did not increase as the dose of estrogen was increased. Because of this experience and the poor results in so many cases, it was concluded that estrogen therapy was not specific for involutional melancholia and that its use would only increase the incidence of recovery or notable improvement. It was suggested, however, that the statistically poor result might be due to the heterogeneity of the population treated.

The cases of these 164 patients were selected from the literature because they satisfied the following criteria:

1. All the patients (with 1 exception) were treated in psychiatric hospitals.

2. All were treated for at least ten weeks, unless recovery occurred earlier.

3. The diagnosis was involutional melancholia in all cases except those in which although a different diagnosis was made, it was clear from the report that the patient was suffering from her first psychosis and that it had occurred within a reasonable time after the onset of the menopause.

4. None of the patients had a history of psychosis earlier in life. Some of the cases described by the authors cited were excluded from the earlier study and from the present investigation because these criteria were not satisfied.

Since the earlier review was written, there has appeared the study of Eyman, Forster, Rivers, Wright and Rome[2] on 180 women with involutional melancholia seen at the University of Pennsylvania. In their cases the diagnosis of involutional melancholia was made without regard to the interval between the onset of the menopause and the onset of the psychosis. In about 18 per cent of their 180 patients the psychosis called involutional melancholia began before the menopause. In another large percentage of patients the menopause antedated the psychosis by many years.

It is interesting to note, also, that the "Statistical Manual for the Use of Institutions for Mental Defectives[3]" includes no reference to the menopause among the criteria for the diagnosis of involutional melancholia, although the syndrome is classified under disorders of metabolism, nutrition and endocrine function.

It is perhaps permissible to assume, therefore, that some investigators have based their diagnoses on the criteria in the "Statistical Manual" without regard to the menstrual history of the patients. Evidence in some of the papers reviewed here supports this assumption. Thus, Wittson,[4] in a study of 272 cases of involutional melancholia, found that "in only 47 per cent of the cases was there a temporal relationship between the menopause and the psychosis."

Among the 164 patients whose cases were previously reviewed, then, there were probably many in whom the psychosis developed either before or many years after the onset of the menopause. Such patients could not reasonably be supposed to be suffering from a psychosis due to estrogen deficiency and could not reasonably be expected to recover with estrogen therapy. I

From the Milwaukee County Hospital for Mental Diseases.

Presented at a meeting of the Milwaukee Neuro-Psychiatric Society, Oct. 28, 1943.

1. Danziger, L.: Estrogen Therapy of Agitated Depressions Associated with the Menopause, Arch. Neurol. & Psychiat. **47**:305 (Feb.) 1942.

2. Eyman, E. V.; Forster, F. M.; Rivers, T. D.; Wright, T. H., and Rome, H. P.: A Statistical Survey of the Biogenesis of Involutional Melancholia, Dis. Nerv. System **3**:16, 1942.

3. Statistical Manual for the Use of Institutions for Mental Defectives, Committee on Statistics of the American Association on Mental Deficiency and The National Committee for Mental Hygiene, ed. 4, New York, 1942.

4. Wittson, C. L.: Involutional Melancholia, Psychiatric Quart. **14**:167, 1940.

believe their inclusion may have accounted for the statistically poor results.

This point may be illustrated by the following example. If a specific therapy is administered to 100 patients, of whom only 50 have the specific disease, not more than 50 can reasonably be expected to recover as a result of the therapy. A few patients with the specific disease ordinarily may not respond, and a few with another disease may recover spontaneously during the period of treatment. The efficacy of the treatment is obscured by the heterogeneity of the group.

In the present instance, in any percentage of the 164 patients presumably suffering from involutional melancholia, the psychosis may have developed coincidentally with the onset of estrogen deficiency. In the absence of individual histories, it is impossible to select from the group those patients for whom the diagnosis of psychosis due to estrogen deficiency is plausible. Fortunately, however, the histories have been reported for some of the 164 patients. The reports previously reviewed and the others which have appeared up to June 30, 1943 [5] have therefore been reconsidered and classified, as follows:

1. In group 1 are the reports of investigators who published the individual histories, including menstrual data. Their patients apparently were suffering from their first psychosis, and the psychosis had developed within a reasonable time after the onset of the presumptive signs of estrogen deficiency, such as hot flashes and irregularity or cessation of the menses. In this matter, considerable allowance must be made for inaccuracies in the histories obtained. It is often difficult for relatives to remember the date of the menopause, and in retrospect there is sometimes a tendency on the part of the family to give undue emphasis to the climacteric.

Data from the reports of group 1 are shown in table 1. In all instances individual histories were contained in the original report.

2. In group 2 are the reports of other investigators in the field. There is no doubt that some of these reports should have been placed in group 1, but from the published data it cannot be said with assurance in which cases the criteria previously enumerated were satisfied. The data for the reports of group 2 are given in table 2.

There is strongly suggestive evidence that the importance of the endocrine disturbances of the climacteric was recognized by some of the investigators [6] whose reports are placed in group 2.

TABLE 1.—*Data on Patients with Psychoses Described as Due to Estrogen Deficiency (Group 1)*

Dose Given in First Month, International Units *	Number of Patients	Patients Recovered or Greatly Improved	Percentage of Patients Recovered or Greatly Improved	Authors
Section 1: Minimal doses				
1,000 to 3,000	3	1		Bowman, K. M., and Bender, L.: Am. J. Psychiat. **11**: 867, 1932.
Totals for section	3	1	33	
Section 2: Moderate doses				
24,000	6	4		Little, G. A., and Cameron, D. E.: Canad. M. A. J. **37**: 144, 1937.
30,000	6	4		Witteon.[4]
45,000	1	1		Suckle, J. E.: J. A. M. A. **109**: 203 (July 17) 1937.
Totals for section	13	9	69	
Section 3: Large doses				
80,000 to 100,000	4	4		Rothermich, N. O.; Postle, B., and Foltz, L. M.: Arch. Neurol. & Psychiat. **45**: 752 (May) 1941.
100,000	2	2		Williams, E. H., and Wright, C. A.: M. Rec. **155**: 11, 1942.
120,000	1	1		Cherry, T. H.: Am. J. Surg. **37**: 302, 1937.
240,000	1	1		Ripley, H. S.; Shorr, E., and Papanicolaou, G. N.: Am. J. Psychiat. **96**: 905, 1940.
80,000 to 600,000	4	4		Levy, W. E.: Tri-State M. J. **10**: 2118, 1938.
80,000 to 600,000	4	4		Dynes, J. B.: Arch. Neurol. & Psychiat. **42**: 248 (Aug.) 1939.
†	7	6		Danziger.[5]
Totals for section	23	22	96	
Grand totals	39	32	82	

* The international unit is about one-third the rat unit.
† Diethylstilbestrol administered by mouth.

5. Some reports have been excluded because it was impossible to determine the amount of estrogen administered or because of other ambiguities.

6. (*a*) Werner, A. A.; Kohler, L. H.; Ault, C. C., and Hoctor, E. F.: Involutional Melancholia: Probable Etiology and Treatment, Arch. Neurol. & Psychiat. **35**: 1076 (May) 1936. (*b*) Ault, C. C.; Hoctor, E. F., and Werner, A. A.: Theelin Therapy in the Psychoses, J. A. M. A. **109**:1786 (Nov. 27) 1937. (*c*) Werner, A. A.; Hoctor, E. F., and Ault, C. C.: Involutional Melancholia, Arch. Neurol. & Psychiat. **45**:944 (June) 1941. (*d*) Davidoff, E.; Reifenstein, E. C., and Goodstone, G. L.: The Treatment of Involutional Psychoses with Diethylstilbestrol, Am. J. Psychiat. **99**:557, 1943.

Inclusion of their figures in table 1 would apparently strengthen the conclusions by increasing the number of cases, but it would introduce an additional subjective factor into the calculations. It was hoped that a separation of the cases, on the single basis of the publication of individual records, would reduce the subjective element of appraisal to a minimum.

In this regard, the reports of Werner and his associates [7] and Davidoff and his associates [6d] should be considered. Werner and his co-improved. Since individual records were not included in the reports of these two series of patients, the results are shown only in table 2.

The material of the two tables is shown graphically in the figure. From analysis of the data represented in the two tables and in the figure, the following statements may be made:

1. With patients whose psychosis was described as due to estrogen deficiency (group 1) large doses gave better results than small doses.

TABLE 2.—*Data on Patients with Psychoses Not Clearly Attributed to Estrogen Deficiency (Group 2)*

Dose Given in First Month, International Units *	Number of Patients	Patients Recovered or Greatly Improved	Percentage of Patients Recovered or Greatly Improved	Authors
Section 1: Minimal doses				
1,500	20	14		Davidson, G. M.: Psychiatric Quart. **13**: 42, 1939.
4,500	34	21		Werner, Kohler, Ault and Hoctor.[6a]
Totals for section	54	35	65	
Section 2: Moderate doses				
12,000	6	0		Schube, P. G.; McManamy, M. C.; Trapp, C. E., and Houser, G. F.: Arch. Neurol. & Psychiat **38**: 505, 1937
30,000 to 40,000	14	11		Ault, Hoctor and Werner.[6b]
25,000 to 30,000	15	0		Notkin, J.: Dennes, B., and Huddart, V.: Psychiatric Quart. **14**: 157, 1940.
25,000 to 50,000	14	6		Hutton, J. H., and Schiller, M. A.: Elgin State Hosp. Papers **3**: 183, 1939.
Totals for section	49	17	35	
Section 3: Large doses				
150,000 to 300,000	22	22		Werner, Hoctor and Ault.[6c]
150,000 to 300,000	14	12		Hawkinson, L. F.: J. A. M. A. **111**: 390 (July 30) 1938.
430,000	15	5		Jones, M. S.; MacGregor, T. N., and Tod, H.: Lancet **1**: 320, 1937.
450,000 to 600,000	63	20		Burlingame, C. C., and Patterson, M. B.: J. Nerv. & Ment. Dis. **94**: 265, 1941
Totals for section	114	59	52	
Section 4: Very large doses				
1,100,000	15	6		Davidoff, Reifenstein and Goodstone.[6d]
*	45	15		Davidoff, Reifenstein and Goodstone.[6d]
*	11	0		Palmer, H. D.; Hastings, D. W., and Sherman, S. H.: Am. J. Psychiat. **97**: 1087, 1941.
Totals for section	71	21	30	
Grand totals	288	132	46	

* Diethylstilbestrol administered by mouth.

workers found that increase in the dose of estrogen improved the results as follows:

Dose, International Units, First Month	No. of Patients	Percentage Recovered or Greatly Improved
4,500	34	61
30,000 to 40,000	14	78
150,000 to 300,000	22	100

In the series of patients whose psychosis Davidoff, Reifenstein and Goodstone described as due mainly to estrogen deficiency, 93 per cent of 15 patients recovered or their condition was greatly

2. With patients whose psychosis was not clearly attributed to endocrine disturbances (group 2) the results did not vary with the dose.

3. With patients in group 1 large doses gave results of the order of magnitude to be expected from specific therapy.[8]

4. With patients in group 2 results of the order of magnitude to be expected from specific therapy were never attained, regardless of the dose.

5. The results shown in table 1 are as satisfactory as can be expected from convulsive

7. Werner, Kohler, Ault and Hoctor.[6a] Ault, Hoctor and Werner.[6b] Werner, Hoctor and Ault.[6c]

8. Burn, J. H.: Errors of Biological Assay, Physiol. Rev. **10**: 146. 1930.

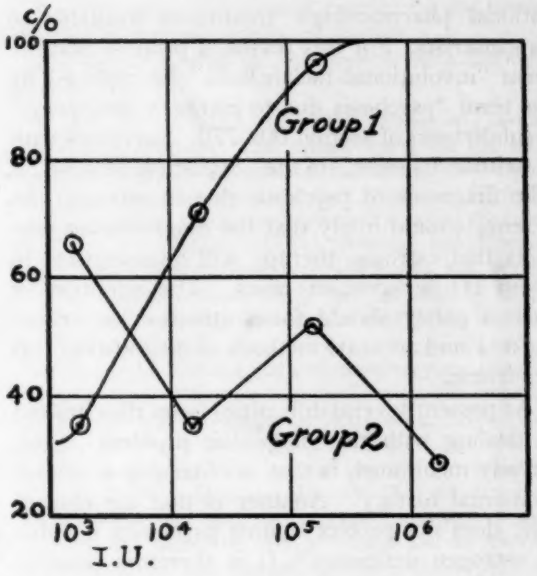
therapy. Estrogen treatment has the additional advantage of safety.

Application of the Pearson chi square test to the figures produce interesting results. It shows that the percentage of 82 in table 1 is significantly different from the percentage of 46 in table 2. This difference admits of at least two interpretations: The patients in the two groups did not receive the same treatment; the patients in the two groups were samples of different populations. The first interpretation, obviously, is contrary to fact. It is apparent, then, that the two groups may have been samples of different populations, only one of which was suffering from psychosis due to estrogen deficiency. By the chi square test, the odds against the identity of the two populations are more than 16,000 to 1.

Previously [1] it was suggested that the group of 164 women was not homogeneous with respect to the disease. By dividing the group into two sections, in accordance with the method described, and by adding to each section the cases reported since Dec. 31, 1940, two samples are obtained, considered respectively in tables 1 and 2. Table 1 appears to deal with a homogeneous sample, by the criteria of bioassay; table 2 probably represents a heterogeneous sample, of which some of the members rightly belong with those described in table 1.

It is perhaps worth while to compare the results shown in table 2 with those to be expected in a control group. For this purpose, the figures of the United States Bureau of the Census [9] are valuable. The published reports for the five year period of 1931 to 1935 were selected because in these years the prognosis was not affected by shock therapy or, to any appreciable extent, by glandular therapy. During this period in all the state hospitals of the United States, 990 women with a psychosis diagnosed as involutional melancholia were admitted each year, and 607 were discharged each year. Of this number, 199 per thousand women admitted for the same psychosis were discharged each year as recovered, and 258 were discharged each year as improved to some degree. The figures given are the means for the five year period. The extremes were 878 to 1,285 patients admitted, 558 to 685 patients discharged, 171 to 224 patients recovered and 233 to 275 improved. Of 1,000 women admitted with a psychosis diagnosed as involutional melancholia, therefore, 457 can be expected to be discharged eventually as recovered or improved.

For the middle year of the period, 1933, the figures for recovery and improvement are reported as functions of the duration of the last hospitalization. In this year, of the women discharged as recovered, 124 had been in the hospital six months or less. In the same year, of the women discharged as improved to any degree, 134 had been in the hospital six months or less. From these figures it is easy to see that of 1,000 women admitted because of involutional melancholia, 125 [10] will be discharged as recovered and 135 will be discharged as improved after a residence in the hospital of six months or less. After the first six months the expectation of recovery or improvement decreases rapidly.



Graphic representation of data on patients in group 1 and in group 2. On the abscissas are plotted the percentages of patients who recovered or showed great improvement; on the ordinates are plotted the approximate doses, expressed in international units, administered during the first month.

In the first six months of hospitalization, therefore, for every 1,000 women admitted a total of 260 women will be discharged as recovered or improved to some degree. The expectation of recovery or improvement in the first six months is, therefore, 26 per cent. But in table 2, 46 per cent of 288 patients recovered or improved notably during the period of therapy, usually much less than six months. By the

9. Mental Patients in State Hospitals, United States Department of Commerce, Bureau of Census, 1931 and 1932; Patients in Hospitals for Mental Disease, ibid., 1933; Patients in Mental Institutions, ibid., 1934, 1935 and 1936.

10. The incidence is calculated to the nearest whole number.

Pearson chi square test, the odds in favor of the significance of the difference between these two percentages are more than 500,000,000 to 1.

From these calculations, it seems safe to say that even in unselected cases of involutional melancholia, estrogen therapy may be expected to increase the incidence of prompt improvement. It should be emphasized that in these calculations spontaneous improvement of any degree was compared with complete recovery or notable improvement with estrogen therapy.

Although the patients referred to in the two tables apparently do not form a homogeneous group, they are now given the same diagnostic label in accordance with the "Statistical Manual." [3] It would seem that such a diagnostic practice obscures the efficacy of one of the rational pharmacologic treatments available to psychiatrists. For this reason, I propose that the term "involutional melancholia" be replaced by the term "psychosis due to estrogen deficiency," a subdivision of section 00x-770, "psychosis with glandular disorder," in the "Statistical Manual." [3] The diagnosis of psychosis due to estrogen deficiency should imply that the diagnostician predicts that estrogen therapy will be successful in about 90 per cent of cases. The adoption of such a policy should focus attention on search for new and accurate methods of diagnosis of this syndrome.

At present several difficulties beset the clinician in dealing with this diagnostic problem. One, already mentioned, is that of obtaining a reliable menstrual history. Another is that the climacteric does not protect against psychoses not due to estrogen deficiency. It is therefore possible for a first mental illness of the schizophrenic, manic-depressive or paranoid type to develop immediately after the menopause. Such an illness, being coincident with, but not due to, estrogen deficiency, cannot be expected to respond to estrogen therapy. A single investigator, in studying a small group of patients, might easily have a large percentage of women with only the psychoses coincident with the menopause. His results with estrogen therapy, then, would be poor, and his figures might depress the percentage of recoveries below the critical level for specificity.

Another source of error should be borne in mind. It is not uncommon for the menstrual periods to cease temporarily shortly before a psychosis, or coincidentally with it. If the patient happens to be at the age at which the menopause is to be expected, this cessation of the menses may be mistaken for the climacteric.

At the Milwaukee County Hospital for Mental Diseases 5 women were selected for treatment with diethylstilbestrol. All had a psychosis diagnosed as involutional melancholia, and clinically the histories of all satisfied the usual criteria for the diagnosis. They had received ordinary hospital care for varying periods, without showing any improvement. In no instance was a clear menstrual history obtained from the hospital records or from special questioning of the relatives. Because of this absence of specific evidence estrogen therapy was begun without much hope of success. It was believed that the patients belonged in group 2 and that the chances of recovery under treatment were not better than even.

All the patients were given a preliminary course of treatments with a placebo for one month, followed by administration of diethylstilbestrol by mouth in the following doses: first month, 1 mg. per day; second month, 2 mg. per day, and third month, 5 mg. per day. None of the patients showed any improvement. Another patient had a clear history which satisfied the criteria proposed for patients in group 1. She showed notable improvement under treatment with diethylstilbestrol. The individual case histories are reported here to illustrate the importance of accurate menstrual records and other evidence of disturbances in the climacteric.

REPORT OF CASES

Case 1.—A. L. was born in 1885. The family history was noncontributory. The patient completed the eighth grade and thereafter worked at home until her marriage. She lived happily with her husband until the onset of the present illness. She was described as shy, sensitive and quiet and devoted to her husband and child and to her household duties.

She was admitted to the Hospital for Mental Diseases on Jan. 17, 1941. Her husband, who gave the history, knew no details of the menstrual record but stated the belief that the patient had been "going through the menopause" during the preceding seven years. He stated that for about seven years, also, she had had numerous somatic complaints and had complained of fear of cancer and blindness. Shortly before admission she accused her husband of infidelity and on one occasion wandered away from home.

On her admission to the hospital the patient was agitated, anxious and depressed. She was also seclusive and tearful. She was afraid she would be transferred to a penal institution. The sensorium was consistent with her education. The physical examination revealed hypertension, without associated heart disease or arteriosclerosis. The laboratory reports indicated nothing significant.

The patient showed no improvement after hospitalization.

Case 2.—E. S. was born in 1886. The family history was noncontributory. The patient completed the sixth grade and thereafter worked as a domestic until her marriage, at the age of 18. She lived happily with her

husband and had 4 children. She was well until the present illness. She was considered good natured, friendly, outgoing and stable. No menstrual history was obtained.

In June 1937 she expressed the belief that she was to be married again, that some one was sending poison through the walls to kill her, that she was to be electrocuted, that her sons were to be turned into women and that doctors and a minister loved her. Because she failed to improve at home, she was admitted to the Hospital for Mental Diseases on Feb. 25, 1938.

On admission the patient was seclusive, confused and hallucinated. She had delusions of reference and of persecution. The sensorium was consistent with her education. Physical examination revealed hypertension and varicose veins but no arteriosclerosis. The results of laboratory studies revealed nothing significant.

The patient adjusted well to life in the hospital but continued to entertain her delusions during the next five years of hospitalization. She failed to respond to estrogen therapy.

CASE 3.—P. B. was born in 1889. The family history was noncontributory. The patient completed the fifth grade and worked for many years as a charwoman. She married at 27, lived happily with her husband and had 1 child. She was well until the present illness. She was described by her daughter as a meticulous housekeeper, who had few friends and no interests outside of the home. No menstrual history was obtained.

The patient's husband died of tuberculosis in March 1937. The patient thereafter complained that the neighbors spied on her, that her daughter had money which she refused to contribute to the family support and that an unidentified man wished to marry her. She threatened suicide and wandered away from home. She was therefore admitted to the Hospital for Mental Diseases on Oct. 27, 1937.

On admission the patient was depressed, seclusive and at times resistive. She expressed suicidal preoccupations and delusions of reference and persecution. The physical examination revealed nothing of interest. The Wassermann reaction of the blood was positive, but that of the spinal fluid was negative. A diagnosis of involutional melancholia complicated by systemic syphilis was made by members of the staff.

After more than four years of hospitalization the patient was still delusional, depressed and at times noisy and destructive. She failed to improve under estrogen therapy.

CASE 4.—C. S. was born in 1892. The family history was noncontributory. She completed the seventh grade and thereafter worked as a waitress until her marriage. Her reaction to her husband's death, in 1927, was considered normal. She was described by her sisters, who gave the history, as quiet, seclusive and sensitive but as well liked by persons who knew her. They stated the belief she "had been going through the menopause" for two years, but they could give no details of the menstrual record.

Eighteen months before admission, the patient accidentally learned that she had syphilis. She became increasingly depressed. No other details were obtained.

On admission to the Hospital for Mental Diseases, on March 22, 1941, she was suspicious, agitated, fearful, depressed and at times noisy. She ate and slept poorly and picked and rubbed her skin. Physical and laboratory studies revealed asymptomatic syphilis. The spinal fluid was normal.

The patient was given metrazol and insulin therapy, without improvement, before she was treated with diethylstilbestrol.

CASE 5.—J. S. was born in 1893. The family history was noncontributory. The patient completed the eighth grade and then worked as a domestic until her marriage, at the age of 18. She was well until the present illness. She was described by her son and husband as good natured, friendly, even tempered and interested in social activities. No definite information as to the menses was obtained. The husband stated the belief that the periods stopped "for a while" after a herniotomy in August 1941 but that they might have returned later.

After the herniotomy the patient became irritable and depressed. She ate little, slept poorly, complained of pain in the back and chest and made two attempts at suicide. She was therefore admitted to the Hospital for Mental Diseases, on Dec. 26, 1941.

On admission she was agitated, depressed and at times mute. She slept poorly and on several occasions had to be fed by tube. The physical examination and laboratory studies revealed nothing of interest.

The patient showed no improvement with hospitalization.

CASE 6.—C. W. was born in 1896. The family history was noncontributory. The patient completed the sixth grade in a parochial school at the age of 16. Thereafter she worked as a grocery store clerk until her marriage to her first, and present, husband, a railway worker, in 1919. No children resulted from the union, which was happy. The patient was well until the present illness. She was described by her husband as happy, friendly and outgoing, interested in church work and in her domestic duties.

In December 1942 she had a hysterectomy and bilateral oophorectomy. The course in the hospital was uneventful, but she never resumed her housework. About two months after the operation hot flashes and general malaise developed. She became increasingly depressed and was afraid to be alone. In June 1943 she expressed suicidal ideas; she said that her condition was hopeless and that she would be only a burden and an expense to her husband. She thought she had a goiter and complained of choking sensations.

On admission to the Hospital for Mental Diseases, on July 20, 1943, she was depressed, agitated and fearful. She became worse rapidly. A month after admission she was mute and negativisitic and frequently had to be fed by tube. She was still agitated and looked extremely depressed.

Three months after admission there had been no improvement. The patient was then started on a course of diethylstilbestrol. One milligram, dissolved in milk, was given each day. After ten days the patient was alert and smiling. She fed herself, ate with good appetite and slept well. After one month she began to speak and was allowed to go home for three day visits. During the second month of treatment, the patient was depressed on the day after her return from each home visit, that is, after three days without medication. At the beginning of the third month of treatment these temporary relapses disappeared. Treatment was stopped at the end of three months.

The patient was then free of complaints and of evidence of depression. She showed some anxiety that her home visits might be discontinued, but this was attributed to her probable intellectual inadequacy.

SUMMARY AND CONCLUSIONS

An analysis of the previously reported use of estrogens in treatment of psychoses indicates that the therapy is specific for patients properly selected in accordance with the clinical criteria given here.

In the absence of accurate evidence of disturbances in the climacteric immediately preceding the psychosis, the chances of recovery with estrogen therapy are not better than even, although the clinical picture may be that of involutional melancholia.

If such patients are given estrogen therapy, however, their chances of prompt improvement are much better than if they receive no special treatment.

The new cases described here illustrate the difficulty of the diagnosis and the importance of a corroborative menstrual history. Five women whose menstrual histories were vague or inadequate failed to improve under treatment with diethylstilbestrol. One woman who had an agitated depression soon after a surgically induced menopause responded dramatically to administration of the substance.

It is suggested that the term "involutional melancholia" in the "Statistical Manual," published by The National Association for Mental Hygiene, Inc., be replaced by that of "psychosis due to estrogen deficiency."

The diethylstilbestrol used in this study was furnished by Dr. D. C. Hines, Eli Lilly and Company, Indianapolis.

Milwaukee County Hospital for Mental Diseases.

BIOCHEMICAL STUDIES ON PATIENTS WITH SCHIZOPHRENIA

DEXTROSE, OXYGEN AND CARBON DIOXIDE CONTENTS OF ARTERIAL AND VENOUS BLOOD FROM THE CRANIAL CAVITY

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In previous biochemical studies on schizophrenia, blood from the cubital vein was used.[1] The present study is concerned with chemical analyses of blood from the femoral artery and the internal jugular vein.

CLINICAL DATA

The significant features in the clinical observations on the 12 patients studied were as follows:

1. All the patients unmistakably had what is called dementia precox, schizophrenia or parergasic reactions.

2. The ages of 8 of the patients were between 18 and 25 at the onset of the illness; 4 patients were, respectively, 25, 26, 28 and 36 years of age.

3. The periods of illness of 10 of the patients prior to the time the chemical analyses were made were from four to twelve months; the length of illness of 1 patient was seventeen months, and that of the other was three years.

4. At the time blood was taken for the chemical study the patients showed no significant emotional disturbances and cooperated in the procedure. Three patients (1, 5 and 6) were free of symptoms; they were discharged as having a social remission a few weeks later (table 1); patient 3 showed improvement in his condition and was discharged shortly afterward, and 8 patients displayed no improvement.

CHEMICAL ANALYSES

Procedure and Methods.—The patient was without breakfast, having had the last meal on the preceding evening. The data were discarded when the patient did not cooperate or was emotionally upset to any notable degree. Arterial blood was obtained from the femoral artery. For puncture of the internal jugular vein (Dr. Haws) the technic described by Myerson, Halloran and Hirsch[2] was used. Oxygen and carbon dioxide contents were determined according to the technic described by Peters and Van Slyke,[3] and the reducing substances, by the usual procedure of Folin.

RESULTS AND COMMENT

Our chemical data are compiled in two tables: Table 1 summarizes the results of analyses of dextrose, oxygen and carbon dioxide; table 2 presents the ranges and averages of these chemical components for our patients, as well as for normal persons, as observed by Gibbs, Lennox, Nims and Gibbs.[4]

A comparison of the data in table 2 follows:

Sugar.—The range of sugar values for both arterial and venous blood was lower for schizophrenic than for normal persons, the difference being more pronounced for venous blood. The range of the differences in the sugar content between arterial and venous blood was considerably wider for schizophrenic patients than for normal subjects, and the average of these differences was notably higher for schizophrenic than for normal subjects. These observations

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Our research on schizophrenia was made possible in part by a grant from the Supreme Council, Thirty-Third Degree Scottish Rite Masons of the Northern Jurisdiction, United States of America.

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2. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular Vein and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

3. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

4. Gibbs, E. L.; Lennox, W. G.; Nims, L. F., and Gibbs, F. A.: Arterial and Cerebral Venous Blood: Arterial-Venous Differences in Man, J. Biol. Chem. **144**:325, 1942.

suggest the following conclusions: The lower sugar content of arterial blood indicates that, other conditions being equal, less sugar is available within the cranial cavity in schizophrenic patients than in normal subjects. The lower sugar content of venous blood is certainly due, at least in part, to the lower sugar content of arterial blood, but it may also be due to a higher assimilation of dextrose by the cerebral or other tissues within the cranial cavity. The assumption that the higher intracranial carbohydrate metabolism in our patients than in normal subjects might be a contributing factor finds support in the higher arteriovenous differences for the patients than for the normal subjects. These suggestions are offered, however, with reservations, for reasons pertaining both to the method of study and to our own material.

In the method of utilizing the differences between the sugar content of arterial blood and that of blood from the internal jugular vein in the study of cerebral metabolism, one should bear in mind that the internal jugular vein, though carrying blood coming mainly from the brain tissues, also receives blood from veins of the meninges and the osseous formations. Other factors which should be considered in any study of metabolism are the speed of circulation of the blood, exchanges between cells and their immediate pericellular environment, and the size of the organ which is the object of the metabolic study —in this case the brain. None of these variables were determined in this study. The limitations inherent in the method of study apply, of course, equally to the other two variables—the oxygen and the carbon dioxide content—analyses for which were made on the same specimens of blood.

With regard to our own data, the very low sugar levels of arterial and venous blood in 1 patient and the particularly high arteriovenous differences for 3 patients (3, 10 and 11), although accounting only partly for the differences in the ranges and averages, should, nevertheless, guard one against generalizations. It is more pertinent to state only that in certain schizophrenic patients less sugar is available within the cranial cavity than in the average normal person; this suggests a relatively lower carbohydrate metabolism in such patients than in the average normal subject. On the other hand, the very high arteriovenous differences for our 3 patients (3, 10 and 11) imply that in certain schizophrenic patients the intracranial carbohydrate metabolism is higher than in the average normal person.

TABLE 1.—*Dextrose, Oxygen and Carbon Dioxide Contents of Blood of Schizophrenic Patients*

Case No.	Dextrose Content of Blood, Mg./100 Cc.			Oxygen, Vol. per Cent			Carbon Dioxide, Vol. per Cent		
	Femoral Artery	Internal Jugular Vein	Arteriovenous Difference	Femoral Artery	Internal Jugular Vein	Arteriovenous Difference	Internal Jugular Vein	Femoral Artery	Venous Arterial Difference
1	92.2	80.2	12.0	20.92	15.47	5.45	54.72	49.92	4.80
2	79.4	68.5	10.9	18.08	14.15	3.93	54.47	45.53	8.94
3	111.7	81.6	30.1	20.08	12.07	8.01	52.80	46.01	6.79
4	....	....	....	19.35	9.02	10.33	57.29	47.81	9.48
5	71.7	62.7	9.0	19.52	14.75	4.77	57.66	51.64	6.02
6	80.0	62.7	17.3	14.08	12.54	1.54	55.30	53.49	1.81
7	77.8	70.9	6.9	15.65	10.80	4.85	59.75	55.00	4.75
8	77.8	65.8	12.0	14.38	12.00	2.38	51.92	51.68	0.24
9	58.0	52.6	5.4	16.09	11.43	4.65	56.04	48.82	7.22
10	86.9	66.6	20.3	20.78	13.07	7.71	57.45	49.02	8.43
11	106.9	64.1	42.8	15.70	12.93	2.77	52.59	46.05	6.54
12	81.0	68.5	12.5	15.28	11.71	3.57	53.51	49.90	3.61

TABLE 2.—*Ranges and Averages for Dextrose, Oxygen and Carbon Dioxide in Blood of Twelve Schizophrenic Patients and Fifty Normal Subjects* *

	Dextrose, Mg./100 Cc.			Oxygen, Vol. per Cent			Carbon Dioxide, Vol. per Cent		
	Femoral Artery	Internal Jugular Vein	Arteriovenous Difference	Femoral Artery	Internal Jugular Vein	Arteriovenous Difference	Femoral Artery	Internal Jugular Vein	Venous Arterial Difference
Schizophrenic Patients									
Range	58-111.7	52.6-81.6	5.4-42.8	12-20.92	9.02-15.47	1.54-10.33	45.53-55	51.92-59.75	0.24-9.48
Average	86.7	67.4	16.2	17.29	12.58	4.60	49.57	55.36	5.72
Normal Subjects									
Range	79-127.0	70-119.0	5-13.0	17.3-22.2	10.6-16.1	4.5-8.5	44.6-50.4	51-57.7	4.4-8.3
Average	92	82	9.8	19.6	12.9	6.7	48.2	54.8	6.6

* Values determined by Gibbs, Lennox, Nims and Gibbs.[4]

Oxygen.—The range of the oxygen content of both arterial and venous blood was somewhat lower for our patients than for normal subjects. This agrees with the lower range of sugar values for arterial and venous blood for our schizophrenic patients. The differences between the arterial and the venous oxygen contents were of a wider range, and the average of the differences was lower, for the patients than for the normal subjects. These data suggest a lower utilization of oxygen by the schizophrenic patients than by the normal subjects. Here, again, it should be noted that the number of patients used in this study and the fact that the lower average arteriovenous difference is largely due to the low differences for 3 patients (6, 8 and 12) do not warrant one's drawing any general conclusion. One is only justified in stating that in certain schizophrenic patients the oxygen metabolism is lower than in average normal subjects.

Carbon Dioxide.—No significant differences appeared between the ranges of the carbon dioxide contents of arterial and of venous blood for our patients and the corresponding ranges for the normal subjects. In contrast to these observations were the much wider range of venous-arterial differences and a somewhat lower average of the differences for our patients than for the normal controls. This lower average of venous-arterial differences in carbon dioxide content for schizophrenic patients than for normal subjects lends support to the postulate derived from some of our observations on the dextrose values, namely, that of a lower carbohydrate metabolism in certain schizophrenic patients than in normal subjects. Here, again, one should be guarded against generalizations, inasmuch as the lower average of venous-arterial differences in carbon dioxide content for our patients was due mainly to the low differences for 4 patients (1, 7, 8 and 12).

SUMMARY AND CONCLUSIONS

The relatively low sugar content of arterial (femoral) and venous (internal jugular) blood for certain schizophrenic patients suggests a lower intracranial carbohydrate metabolism in these particular patients than in normal subjects, as determined by Gibbs, Lennox, Nims and Gibbs.[4] On the other hand, the higher differences in the sugar contents of arterial and venous blood for certain schizophrenic patients than for normal subjects suggest a more intense carbohydrate metabolism in the former than in the latter.

In certain schizophrenic patients the intracranial oxygen metabolism is lower than in normal subjects.

The lower average venous-arterial difference in carbon dioxide content for our schizophrenic patients than for normal subjects lends support to the postulate of a lower carbohydrate metabolism in certain schizophrenic patients than in normal subjects.

Our conclusions are offered with reservations, for reasons pertaining both to the method of study and to our own material.

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CEREBRAL METABOLISM IN HYPOXIA

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The experiments to be reported were undertaken in order to study the effects of varying degrees of hypoxia on the metabolism of the brain. Since formation of lactic acid and decomposition of phosphocreatine are known to occur in cerebral tissue under conditions of oxygen lack,[1] it seemed pertinent to find the critical oxygen levels at which these changes begin. Gas mixtures low in oxygen were administered to dogs for periods of fifteen to sixty minutes, and chemical studies of parts of the cerebral cortex were made by the technic of freezing the brain in situ with liquid air prior to removal of specimens for analysis. The freezing suddenly stops all metabolic processes in the tissue and prevents the occurrence of postmortem changes. The resultant chemical pattern gives an indication of the metabolic conditions within the tissue at the time of freezing.

The cerebral arteriovenous differences in oxygen and carbon dioxide were measured at the different levels of arterial oxygenation. The blood pressure and the respiratory rate were recorded throughout each experiment. The chemical changes in the cerebral tissue were correlated with changes in the electrocorticogram observed at various oxygen levels in other dogs.

PROCEDURE

Material.—Mongrel dogs weighing between 5 and 15 Kg. were used. Analgesia was induced with morphine sulfate, in doses of 20 mg. per kilogram of body weight, and infiltration with 0.25 per cent procaine hydrochloride was used for exposure of vessels and other operative procedures. A Magill intratracheal tube with a Waters-Guedel type of inflatable cuff was inserted into the trachea to provide a patent airway without leakage. The blood pressure was recorded from the femoral artery and the respiration from a balloon about the thorax or from the intratracheal tube.

The skull was exposed through a median incision, and the masseter muscles were reflected laterally. A trephine opening was made over the sagittal sinus, and the bone of the calvarium was cut away until the superior lateral aspects of both hemispheres were exposed. The dura was opened and reflected. Specimens of blood were drawn over mercury from the femoral artery and from the sagittal sinus.

For the administration of gas mixtures,[2] flows of oxygen and of nitrogen were measured by means of Foregger wet flow meters and delivered to a 5 liter breathing bag. The other end of the breathing bag was connected to the intratracheal tube and to the expiratory system, which consisted of an 18 mm. tube with the end immersed to a depth of 2 cm. in water contained in an open vessel. This kept the bag filled but not distended. A directional valve prevented rebreathing from the expiratory tube. The volume of gas passing through the bag and out the respiratory tube (5.8 to 8.8 liters per minute) was deemed sufficient to prevent accumulation of carbon dioxide.

At the chosen time the final specimens of blood were taken, and the brain was then immediately frozen in situ[3] with liquid air.[4] A specimen of tissue was obtained from each of the cerebral hemispheres. The specimens included parts of the postcruciate, coronal, ectolateral, suprasylvian and ectosylvian gyri.

For the purpose of studying the effects of hypoxia on the electrocorticogram, animals were prepared a day or more in advance by insertion of the electrodes under anesthesia induced with pentobarbital sodium. Into a threaded drill opening in the skull was screwed a plastic plug with a central core of solder, which made contact with the dura and was fused to a wire lead. Two electrodes were used in each animal, which made contact with the left and the right parieto-occipital region. Monopolar recordings were made with a Garceau two channel electroencephalograph.[5]

Chemical Methods.—The oxygen content and capacity and the carbon dioxide content of the blood were determined manometrically by the methods of Van Slyke and Neill.[6] Analyses of gas mixtures with the same apparatus served to calibrate the wet flow meters for oxygen

From the Department of Surgery, Wayne University College of Medicine.

1. Stone, W. E.; Marshall, C., and Nims, L. F.: Chemical Changes in the Brain Produced by Injury and by Anoxia, Am. J. Physiol. **132**:770 (April) 1941.

2. Dr. Ivan B. Taylor and Dr. George F. Browne, of the department of anesthesiology, arranged the apparatus for the administration of oxygen-nitrogen mixtures.

3. Kerr, S. E.: Studies on the Phosphorus Compounds of the Brain: I. Phosphocreatine, J. Biol. Chem. **110**:625 (Aug.) 1935.

4. The liquid air was supplied by the Wall Chemicals Division of the Liquid Carbonic Corporation, Detroit.

5. Miss Marjorie Wade, of the department of electroencephalography of Grace Hospital, assisted with the electroencephalographic recordings.

6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: II. Methods, Baltimore, Williams & Wilkins Company, 1932.

and nitrogen.[7] Lactic acid was determined by the method of Barker and Summerson.[8] The methods used for fractionation and determination of the acid-soluble phosphorus compounds have previously been described.[9]

RESULTS

Respiration, Blood Pressure and Reflexes.—The observed effects of hypoxia on the respiration and blood pressure in the morphinized dog were essentially the same as the effects of lack of oxygen under other conditions described by numerous authors.[10] Inhalation of 13 per cent oxygen produced mild hyperventilation, which was increased with increasing degrees of hypoxia. At oxygen levels of 5 per cent or less the initial hyperventilation was followed by slowing of the respiratory rate, with a further increase in depth of the respiratory movements. Later the respirations became shallow. On readmission of air in recovery experiments there occurred a sudden depression of depth and frequency, followed by gradual recovery. After the animal had breathed room air for twenty to thirty minutes, panting respiration usually supervened. Figure 1 shows the changes in respiration and blood pressure in a typical experiment.

With oxygen levels below 6 per cent the blood pressure usually showed an initial increase, followed by a decrease approaching, and in some instances dropping a little below, the original level. The pulse rate showed only minor changes during hypoxia but was greatly increased in the early part of the period of recovery.

In 2 animals a progressive decrease in blood pressure occurred during the period of oxygen lack.

With severe hypoxia diminution in the reactivity of the reflexes of the cornea and lids usually occurred.

Appearance of the Cortex and Operative Wound.—With severe degrees of hypoxia the cortex darkened visibly, and there was notable engorgement of the vessels of its surface. The operative wounds usually began to bleed profusely from the muscle and dural vessels, and in some instances from the needle opening in the sagittal sinus. On readmission of air the normal appearance of the cortex returned and bleeding ceased.

Levels of Oxygen and Carbon Dioxide in the Blood.—The accompanying table gives the results of analyses of specimens of blood drawn just before the brain was frozen. For recovery experiments there are included data on additional analyses of specimens obtained just before the hypoxia was terminated. The initial levels of oxygen and carbon dioxide were in the normal range and have been omitted from the table.

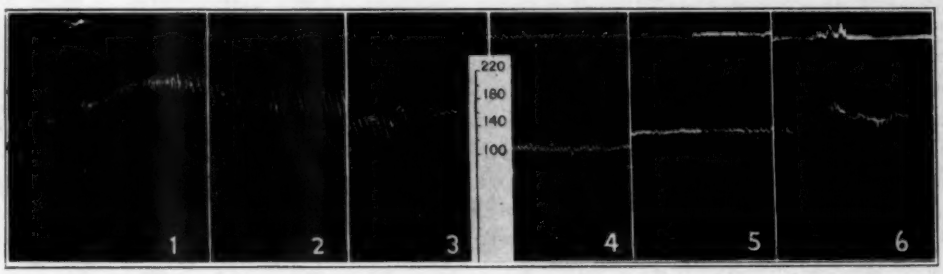

Fig. 1 (dog 128).—Respiration (upper record) and blood pressure (lower record) during hypoxia and recovery. *1*, beginning of administration of 4.2 per cent oxygen; *2*, after ten minutes of hypoxia; *3*, admission of room air after twenty-four minutes of hypoxia; *4*, ten minutes after admission of air; *5*, twenty minutes after admission of air; *6*, forty minutes after admission of air.

A decrease in the carbon dioxide content of the blood was always observed at oxygen levels below 7 per cent in the inspired air and frequently also with the milder degrees of hypoxia. Two factors operating to produce this change were the increase in the lactate of the blood (which replaces bicarbonate) and the hyperventilation.

The cerebral arteriovenous differences in oxygen and carbon dioxide were decreased at the lower levels of oxygenation. Courtice[11] reported similar results in cats. This change is probably due in part to a decrease in the cerebral oxidation rate and in part to an increase in the

7. The gasometric determinations were performed by Mr. Joseph Kopala.

8. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535 (April) 1941.

9. Stone, W. E.: Acid-Soluble Phosphorus Compounds of Cerebral Tissue, J. Biol. Chem. **149**:29 (July) 1943.

10. (*a*) Gellhorn, E.: Autonomic Regulations, New York, Interscience Publishers, Inc., 1943. (*b*) Van Liere, E. J.: Anoxia: Its Effect on the Body, Chicago, University of Chicago Press, 1942.

11. Courtice, F. C.: The Effect of Oxygen Lack on the Cerebral Circulation, J. Physiol. **100**:198 (Sept. 8) 1941.

cerebral blood flow. Gibbs and associates [12] observed an increase in the cerebral blood flow in human subjects subjected to hypoxia, and Dumke and Schmidt [13] obtained the same results in monkeys.

Cerebral Changes During Hypoxia of Fifteen Minutes' Duration.—The values for fifteen minute periods of hypoxia are included in the table and are illustrated in figure 2. The shaded areas indicate the ranges in which the values fall. Cerebral lactic acid begins to increase when the oxygen in the respired air is reduced to 11 to 13 per cent, a level corresponding to an oxygen saturation of arterial blood of 55 to 65 per cent. The oxygen saturation of blood in the sagittal sinus at this level is 28 to 43 per cent.

The inverse changes in phosphocreatine and inorganic phosphate indicate hydrolysis of phosphocreatine, beginning at a level of approximately 7 per cent oxygen in the respired air, or an oxygen saturation of arterial blood of 23 to 35 per cent. The oxygen saturation of the blood in the sagittal sinus is 15 to 22 per cent at this level, and the arteriovenous difference in oxygen content begins to decrease.

Cerebral Metabolism in Animals with Hypoxia

Dog No.	Oxygen-Nitrogen Mixtures Breathed: Percentage of Oxygen	Oxygen-Nitrogen Mixtures Breathed: Min.	Blood from Femoral Artery: Oxygen Capacity, Volume per Cent	Blood from Femoral Artery: Oxygen Saturation, Percentage	Blood from Femoral Artery: Carbon Dioxide Content, Volume per Cent	Blood from Femoral Artery: Plasma Lactic Acid, Mg. per 100 Gm.	Blood from Sagittal Sinus: Oxygen Saturation, Percentage	Blood from Sagittal Sinus: A-V Differences: Oxygen, Volume per Cent	Blood from Sagittal Sinus: A-V Differences: Carbon Dioxide, Volume per Cent	Cerebral Tissue: Lactic Acid, Mg. per 100 Gm.: Right Cortex	Cerebral Tissue: Lactic Acid, Mg. per 100 Gm.: Left Cortex	Cerebral Tissue: Inorganic Phosphorus, Mg. per 100 Gm.: Right Cortex	Cerebral Tissue: Inorganic Phosphorus, Mg. per 100 Gm.: Left Cortex	Cerebral Tissue: Phosphocreatine Phosphorus, Mg. per 100 Gm.: Right Cortex	Cerebral Tissue: Phosphocreatine Phosphorus, Mg. per 100 Gm.: Left Cortex
19	21	..	25.7	97.2	40.1	..	....	...	...	10.2		8.2		10.2	
21	21	..	22.4	86.2	35.6	..	73.0	+3.9	—3.5	11.6		7.2		11.0	
107	21	..	23.2	82.5	48.6	49	49.8	7.6	7.4	17.2	12.1	8.7	6.9	7.8	8.7
113	21	..	20.3	94.7	33.4	30	60.7	6.9	5.9	9.5	9.5	6.6	7.4	9.6	8.9
99	13.0	15	20.3	70.0	40.3	..	....	...	...	9.1	10.2	7.0	6.2	10.3	9.7
100	13.0	15	21.8	56.9	41.2	38	28.7	6.0	6.4	16.8	14.0	7.7	...	11.2	...
104	13.0	15	21.9	66.2	45.7	..	33.6	7.1	7.8	14.4	12.9	8.6	8.7	7.4	7.8
101	11.6	15	19.6	61.3	43.6	16.9	42.3	3.7	3.8	20.7	20.2	9.5	8.9	8.7	8.9
96	10.2	15	26.4	40.2	51.1	41	....	...	...	33	34	7.7	8.7	8.3	7.6
98	10.2	15	23.6	34.7	38.2	43	21.3	3.2	10.4	40	47	8.6	7.7	7.9	8.7
87	8.8	15	25.0	38.4	41.3	..	....	...	...	34	33	7.8	6.8	9.2	9.0
97	8.8	15	24.5	47.3	44.4	66	24.2	5.7	5.7	34	30	7.2	6.8	10.6	10.3
89	7.4	15	17.8	54.0	33.7	..	....	...	...	55	53	7.9	7.2	7.7	7.3
95	7.4	15	24.7	44.8	44.4	46	....	...	...	64	67	8.5	9.9	9.3	8.1
96	6.6	15	24.6	22.7	43.3	39	24.0	—0.3	0.3	55	51	9.4	8.3	7.5	7.9
90	5.8	15	25.2	13.5	34.9	106	8.7	+1.3	1.3	72	77	9.7	9.0	7.6	7.3
92	5.8	15	23.1	19.9	40.2	95	....	...	...	95	84	11.4	10.3	5.7	5.9
94	5.8	15	26.6	19.5	49.2	70	12.2	2.0	0.3	90	78	10.5	10.1	5.5	6.5
102	5.0	15	18.0	22.8	28.5	76	13.9	1.6	4.1	70	76	8.6	9.4	7.5	7.2
103	4.2	15	22.5	16.0	16.9	112	....	...	...	114	116	11.7	10.4	4.3	4.5
106	4.2	15	23.2	14.7	35.4	76	....	...	...	93	89	10.1	9.6	5.9	5.5
81*	7.4	14	18.8	30.3	33.6	..	....	...	...	122		12.0		3.1	
105*	4.2	15	24.2	13.6	21.1	198	5.9	1.9	6.7	157	167	13.9	15.4	3.0	2.5
108	11.6	60	22.8	49.1	40.1	34	26.1	5.3	5.7	18.6	15.7	9.1	7.9	8.6	9.0
110	7.4	60	19.5	26.1	27.8	107	....	...	...	48	48	9.0	8.4	7.3	7.6
111	7.4	60	....	....	....	66	....	...	...	49	45	7.7	7.9	7.4	7.1
118	7.4	15	23.2	38.8	37.6	39	22.0	3.9	4.2	....	....	...	...	....	....
	21	10	23.2	83.6	42.1	27	54.3	6.8	4.5	19.9	17.2	8.4	8.0	10.9	10.5
119	7.4	15	20.0	53.5	31.8	44	25.5	5.6	7.1	....	....	...	...	....	....
	21	10	20.0	75.5	37.3	42	43.5	6.4	5.3	13.5	15.8	7.2	7.5	11.2	10.8
114	4.2	15	23.4	16.2	22.4	..	....	...	...	....	....	...	...	....	....
	21	5	23.4	85.5	21.6	99	....	...	...	90	71	6.1	5.7	8.1	9.8
116	4.2	20	19.7	11.2	12.8	152	4.3	1.4	4.0	....	....	...	...	....	....
	21	13	19.7	92.0	20.6	117	67.6	4.8	0.8	90	66	7.6	8.0	8.0	8.5
128	4.2	24	20.5	13.1	15.4	243	8.3	1.0	7.0	....	....	...	...	....	....
	21	46	20.5	93.7	43.1	47	51.7	8.6	12.4	19.2	25.8	7.7	8.1	8.8	8.0

* These dogs had low blood pressure during hypoxia.

The data on the 2 animals (dogs 81 and 105) in which low blood pressure obtained are included in the table but were omitted from figure 2. The chemical changes in the brains of these animals were disproportionately large, undoubtedly the result of a decrease in the blood supply to the brain.

Cerebral Changes During Hypoxia of One Hour's Duration.—Prolongation of the period of oxygen deprivation to one hour in three experiments did not cause further changes in the cerebral constituents studied, although these experiments were carried out at critical levels for the beginning of changes in lactic acid or phosphocreatine (table). This indicates that within

12. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Changes in Human Cerebral Blood Flow Consequent on Alterations in Blood Gases, Am. J. Physiol. **111**:557 (April) 1935.

13. Dumke, P. R., and Schmidt, C. F.: Quantitative Measurements of Cerebral Blood Flow in the Macaque Monkey, Am. J. Physiol. **138**:421 (Feb.) 1943.

the fifteen minute period a steady state is attained in which further accumulation of lactic acid does not occur. Since the level of lactic acid was higher in the blood than in the brain in these experiments, it cannot be assumed that lactic acid was continuously being formed in the brain and removed by the blood.

Relation of Lactic Acid of the Brain to That of the Blood.—The lactic acid of the brain was higher than that of the blood in some instances and was lower in others. This difference is evident from the values given in the table, and it has been observed also with experimental head injury and other conditions. These data confirm previously published evidence [14] that the level of

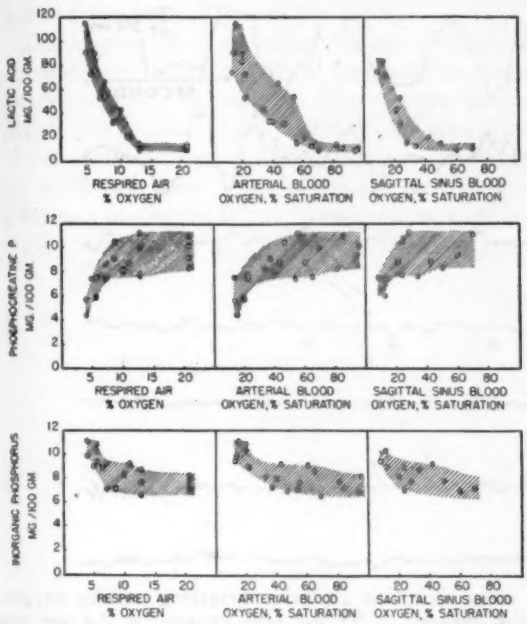
LACTIC ACID MG./100 GM.
PHOSPHOCREATINE P MG./100 GM.
INORGANIC PHOSPHORUS MG./100 GM.
RESPIRED AIR % OXYGEN
ARTERIAL BLOOD OXYGEN, % SATURATION
SAGITTAL SINUS BLOOD OXYGEN, % SATURATION

Fig. 2.—Values for lactic acid, phosphocreatine and inorganic phosphate in the brain during hypoxia of fifteen minutes' duration.

lactic acid in the brain is independent of the level in the blood. Other workers have shown that the "hematoencephalic barrier" is relatively impermeable to anions [15] and that lactic acid is largely ionized at the p_H of the blood. It need not be inferred that diffusion of lactate between the blood and the brain does not occur; it is only pointed out that the rate of diffusion is much slower than the rates of the metabolic reactions in which lactate participates, so that the level of lactic acid in the brain is regulated primarily by metabolic conditions within the cells.

14. Stone, W. E.: The Effects of Anaesthetics and of Convulsants on the Lactic Acid Content of the Brain, Biochem. J. **32**:1908 (Nov.) 1938.

15. Friedemann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125 (April) 1942.

Adenosine Triphosphate and "Residual Phosphorus" Fractions.—No significant changes occurred in the adenosine triphosphate of the cerebral tissue during hypoxia. Normal levels were found in animals with the most severe degrees of oxygen deficiency studied, even in the 2 dogs in which the blood pressure was lowered and in the animals in which the period of hypoxia was extended to one hour. The absence of pentose-containing products of decomposition was also noted. This is in striking contrast to the decomposition which occurs in postmortem tissue.[16] Apparently the complete phosphorylation of the nucleotide is maintained as long as any phosphocreatine is still present, as is to be expected from the equilibrium constants reported by Lehmann.[17]

The acid-soluble phosphorus compounds of cerebral tissue include some "residual organic phosphorus," which can be separated into at least three fractions.[9] None of these has as yet been identified with certainty, though one appears to be hexose-6-monophosphate. It was found that hypoxia did not cause significant changes in these fractions.

Recovery from Hypoxia.—In five experiments the hypoxia was terminated by administration of room air for recovery periods of five to forty-six minutes (table). Reoxygenation of the blood was satisfactory, and resynthesis of phosphocreatine was complete in every instance. After a moderate degree of hypoxia (7.4 per cent oxygen in the inspired air) the return of the lactic acid to its normal level was practically complete in ten minutes. With severe hypoxia (4.2 per cent oxygen) the lactic acid decreased only a little during the early part of the recovery period (five to thirteen minutes) but was approaching the normal value in forty-six minutes.

The Electrocorticogram in Relation to Chemical Changes.—The electrocorticogram of the morphinized dog showed a dominant frequency of 20 to 26 per second. The changes observed during hypoxia were in agreement with the results of other investigators under different conditions.[18] When the oxygen in the respired air was reduced to 13 per cent, a definite increase in amplitude usually occurred. This change therefore preceded the increase in lactic acid in the brain. Administration of 11.6 per cent oxygen

16. Kerr, S. E.: Studies on the Phosphorus Compounds of Brain: III. Determinations of Adenosine Triphosphate and Its Decomposition Products in Fresh and Autolyzed Dog Brain, J. Biol. Chem. **145**:647 (Oct.) 1942. Stone.[9]

17. Lehmann, H.: Ueber die Umesterung des Adenylsäuresystems mit Phosphagenen, Biochem. Ztschr. **286**: 336, 1936.

(Footnote continued on next page)

for fifteen minutes resulted in a decrease in frequency. Thus the slowing of the waves corresponds closely with the beginning of the rise in cerebral lactic acid. At still lower oxygen levels the slow waves dominated the pattern, their frequency decreasing and their amplitude increasing progressively with the decrease in oxygen tension (fig. 3).

Gibbs and Gibbs [18] found that slowing of the electrical activity of the human brain begins when the oxygen saturation of the cerebral venous blood is reduced to 30 per cent. It is notable that the same change in electrical activity occurs in the dog at levels of 28 to 43 per cent oxygen saturation of the blood of the sagittal sinus.

of pure nitrogen, electrical activity is silenced when the phosphocreatine is only mildly decreased.[1] It should be noted, however, that conduction by nerve fibers and synapses is not immediately inhibited by lack of oxygen.[10b] Possible effects of changes in the chemical milieu on synchronizing mechanisms in the brain must be kept in mind. The influence of peripheral systems on the cortical activity may also be modified by hypoxia.

The time required for recovery of the electrocorticogram to normal after a period of hypoxia appears to vary with the degree and the duration of the oxygen deficiency. Recovery is almost immediate after two to three minutes of hypoxia,

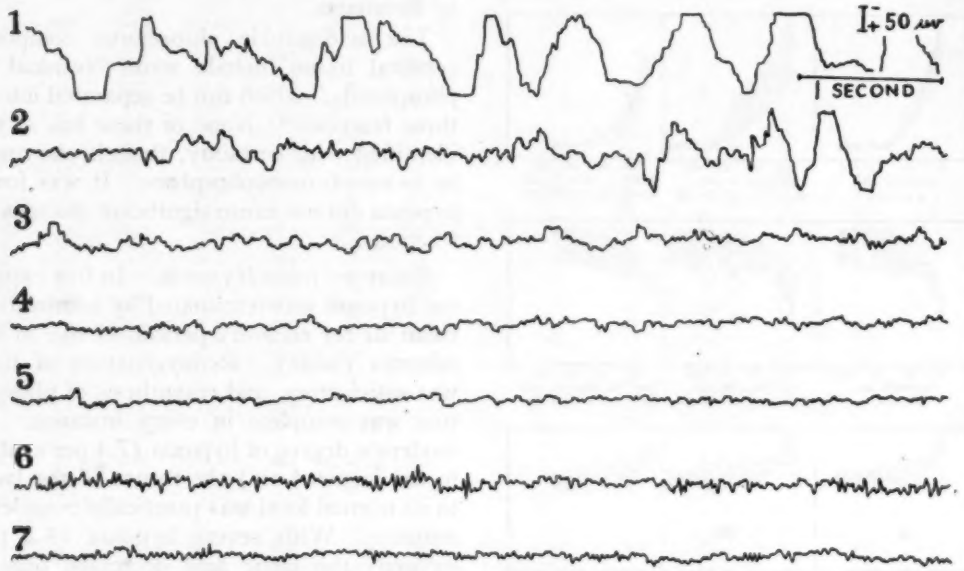

Fig. 3.—The electrocorticogram during hypoxia in dogs under morphine analgesia, breathing various oxygen-nitrogen mixtures for six to fifteen minutes: *1*, 4.2 per cent oxygen; *2*, 5.8 per cent oxygen; *3*, 7.4 per cent oxygen; *4*, 8.8 per cent oxygen; *5*, 10.2 per cent oxygen; *6*, 13 per cent oxygen, and *7*, room air.

The occurrence of changes in the electrocorticogram during hypoxia before the store of phosphate bond energy has begun to decrease, and while the glycolytic system is able to contribute energy for phosphorylation, suggests that the function of oxygen in relation to the electrocorticogram involves more than the supply of oxidative energy for phosphorylation. With inhalation

but after administration of 4.2 per cent oxygen for fifteen minutes the return to normal requires as long as an hour in some instances. Further experiments are necessary to determine whether or not a direct relation exists between the changes in the electrocorticogram and those in the level of lactic acid during the period of recovery.

Since hypoglycemia alters the response of the electrocorticogram to hypoxia,[10a] it should be noted that the levels of the blood sugar were found to be higher than normal in the experiments reported here. Morphine, as well as hypoxia, tends to increase the blood sugar.

It is well known that the pattern of the electrocorticogram is profoundly influenced by the carbon dioxide tension in the brain [18] and that carbon dioxide antagonizes the effects of hypoxia on cerebral functions.[10a] The influence of carbon

18. Davis, H., and Davis, P. A.: The Electrical Activity of the Brain: Its Relation to Physiological States and to States of Impaired Consciousness, A. Research Nerv. & Ment. Dis., Proc. (1938) **19**:50, 1939. Gellhorn.[10a] Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941. Gibbs, F. A.; Williams D., and Gibbs, E. L.: Modification of the Cortical Frequency Spectrum by Changes in Carbon Dioxide, Blood Sugar and Oxygen, J. Neurophysiol. **3**:49 (Jan.) 1940. Van Liere.[10b]

dioxide tension on the chemical changes in the brain during hypoxia cannot be evaluated from the data at hand, but further studies with varying carbon dioxide levels are contemplated.

SUMMARY

Chemical changes in the brain were observed in morphinized dogs breathing mixtures low in oxygen for periods of fifteen to sixty minutes.

Below a critical level of 11 to 13 per cent of oxygen in the respired air, the cerebral lactic acid increased with a decreasing supply of oxygen to the brain. The oxygen saturation of the arterial blood at the critical level was 55 to 65 per cent, and that of the cerebral venous blood, 28 to 43 per cent. The level of lactic acid in the brain was independent of that in the blood.

Decomposition of phosphocreatine occurred in the cerebrum below a critical level of 7 per cent oxygen in the respired air. The oxygen saturation of the arterial blood at this point was 23 to 35 per cent, and that of the cerebral venous blood, 15 to 22 per cent. The cerebral arteriovenous difference in oxygen began to decrease at approximately this level.

Prolongation of the period of hypoxia from fifteen minutes to one hour did not modify the extent of the chemical changes noted.

No decomposition of cerebral adenosine triphosphate occurred with even the most severe degrees of hypoxia studied.

Resynthesis of phosphocreatine was complete within five minutes after readmission of room air in animals with the most severe degrees of hypoxia studied. The lactic acid decreased more slowly, approaching the normal level in ten minutes after a period of breathing 7.4 per cent oxygen and in forty-six minutes after a period of breathing 4.2 per cent oxygen.

The electrocorticogram showed an increase in amplitude on administration of 13 per cent oxygen, i. e., at a degree of hypoxia too mild to produce an increase in cerebral lactic acid. With 11.6 per cent oxygen a definite slowing of the waves and a decrease in amplitude became evident. This change, therefore, occurred at the critical level for the beginning of the rise in lactic acid.

Wayne University College of Medicine.

Clinical, Technical and Occasional Notes

REGULAR FORTY TO FIFTY DAY CYCLE OF PSYCHOTIC BEHAVIOR IN A 14 YEAR OLD BOY

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Regular cyclic variations in behavior have been produced or abolished in experimental animals by surgical interference with the function of one or another of the endocrine glands, and the results indicate that each gland functions with a specific frequency. For example, it has been shown that the regular four to five day cycles of spontaneous activity manifested by rats were definitely associated with the cyclic variations in ovarian function.[1] Further, section of the pituitary stalk in rats often brought out regular cycles in activity and food and water intake, with an average frequency of fourteen days [2]; removal of the parathyroid glands brought out a twenty day cycle of activity in rats and a forty day cycle of activity and calcium appetite in monkeys [3]; thyroidectomy brought out a twenty-five to thirty-five day cycle of activity in rats,[4] and removal of one ovary and partial removal of the other, with traumatization of the remaining tissue, brought out a one hundred day cycle of activity in rats.[5]

In clinical material psychiatric observers have given particular attention to cyclic variations in behavior, often on the assumption that such periodicity has hormonal determinants. The menstrual cycle has been most carefully studied in this regard.

On the basis of the demonstration that in animals the function of an endocrine gland may be associated with a cyclic variation in behavior of specific frequency, a renewed study has been made of cyclic variations in human beings, particularly psychiatric patients. In this study an attempt is made to determine (1) to what extent the behavior cycles have a constant and specific frequency and (2) to what extent these cycles may be associated with disturbances in one or another of the endocrine glands.

Opportunities to observe long term behavior cycles in psychiatric patients are relatively rare. It is only in clinics in which detailed daily records of behavior are kept, and which are staffed with well trained nurses, that full observations can be made. Even then, many a patient manifesting such cyclic variations in behavior escapes attention unless he is placed under special study. The scarcity of the opportunities, I feel, justifies the report of individual cases in which regular cycles occur.

The following case is that of a 14 year old boy who over a period of observation of eight and a half months in the Phipps Clinic of the Johns Hopkins Hospital showed nearly regular cycles of variation in behavior, with a frequency of forty to fifty days.

HISTORY OF CASE

E. H. L., a Jewish American school boy aged 14, was brought to the Henry Phipps Psychiatric Clinic on Dec. 26, 1941, after six days of excited, unmanageable behavior at home. He was the older of 2 siblings, born of an American Jewish college professor and a Russian Jewish registered nurse. The home atmosphere had always been marked by wrangling between the parents, with much shouting and screaming and little or no disciplinary restraint over the children. The 10 year old sister had been seen in the Harriet Lane Home for Children as a "problem child." There was no family history of epilepsy or of any psychosis.

Examination at the time of admission revealed that the patient was a rather attractive youth of athletic habitus, who appeared more nearly 18 than 14 years of age and was physically well developed (height, 5 feet 10½ inches [179 cm.]; weight, 140 pounds [63.5 Kg.]) and sexually mature. There were no significant physical abnormalities. He manifested pronounced overactivity, was distracted readily, moved constantly and talked boastfully. He explained that he had three jobs, was making $5,200 a year, was going to be dictator of the world and would give the physician $100,000.

Previous to the present illness the patient had always been an essentially healthy and very gifted boy, doing outstanding work in school, excelling in athletics and showing distinct musical aptitude. He had heard much discussion of his superior intelligence since 1939, when

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From the Psychobiological Laboratory, Phipps Psychiatric Clinic.

This study was supported by a grant made to Dr. Curt P. Richter by the Committee for Research in Endocrinology.

1. Wang, G. H.: The Relation Between "Spontaneous" Activity and Oestrous Cycle in the White Rat, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1923, vol. 2, no. 6.

2. Richter, C. P.: Cyclical Phenomena Produced in Rats by Section of the Pituitary Stalk and Their Possible Relation to Psuedo-Pregnancy, Am. J. Physiol. **106**:80 (Oct.) 1933.

3. (*a*) Richter, C. P., and Eckert, J. F.: Increased Calcium Appetite of Parathyroidectomized Rats, Endocrinology **21**:50 (Jan.) 1937. (*b*) Richter, C. P.; Honeyman, W. M., and Hunter, H.: Behaviour and Mood Cycles Apparently Related to Parathyroid Deficiency, J. Neurol. & Psychiat. **3**:19 (Jan.) 1940.

4. Richter, C. P.: The Role Played by the Thyroid Gland in the Production of Gross Body Activity, Endocrinology **17**:73 (Jan.-Feb.) 1933.

5. Wang, G. H., and Guttmacher, A. F.: The Effect of Ovarian Traumatization on the Spontaneous Activity and Genital Tract of the Albino Rat, Correlated with a Histological Study of the Ovaries, Am. J. Physiol. **82**:335 (May) 1927.

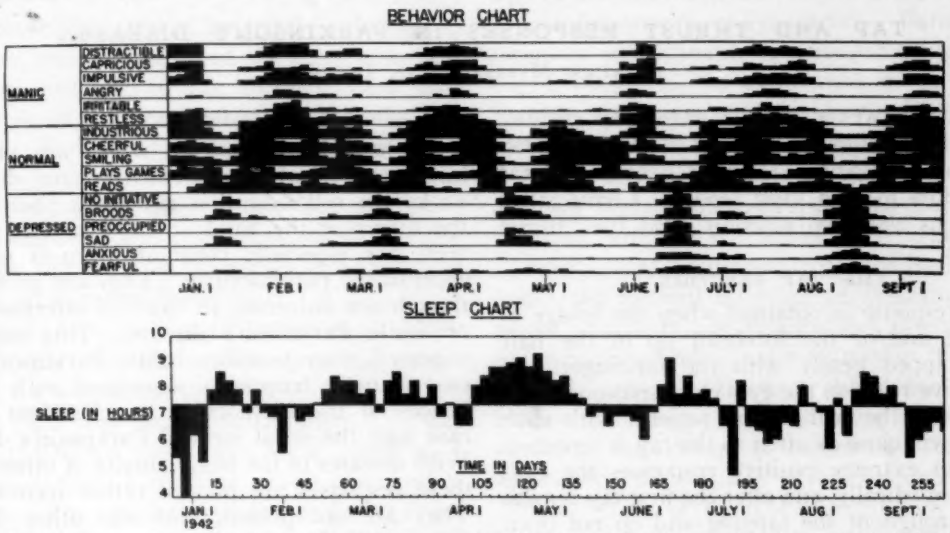
his intelligence quotient was reported to be 153. Both parents were frankly ambitious for him and pushed him into intellectual and social activities beyond his years and economic level.

The present illness probably started during the summer preceding admission, while the patient was attending an exclusive summer camp. Among the precipitating factors were his reaching sexual maturity at this time and soon thereafter meeting a wealthy non-Jewish girl in whom he became interested. When he came home in the fall, he became depressed when the family made it clear that they could not live up to the girl's economic standards—in particular, that it was not possible to send him to a private school. He was accordingly sent back to the local public high school, where, in contrast to his previous record, his attendance was irregular and his work poor. During the four months between the opening of the school year and his admission to the clinic, there were pronounced swings in mood, varying from worry over the racial problem and the war to excitement about the possibility of his making money by selling sandbags to local merchants.

phases rarely lasted more than a few days. The transition from one phase to another was usually rapid, especially during the early cycles, sometimes requiring less than forty-eight hours. Similar sharp transitions in mood and behavior have been observed in patients who showed regular two day cycles of alternating good and bad behavior.[6]

The sleep chart presents the amount of sleep in terms of hours above and below seven and a half hours. This record shows the same forty to fifty day cycles, with short hours of sleep during manic phases and surprisingly long hours of sleep during depressed phases. The periods of sleep ranged from four to nine hours. Patients with the two day cycles of behavior and sleep also showed the same inverse relation between the number of hours of sleep and the phases of manic behavior.

While in the elated state the patient frequently "fired" the ward physician and the entire nursing staff, was loud, profane and actively belligerent toward other patients and attendants, was vulgar and obscene and was often careless of his excreta. During such episodes



Behavior and sleep chart for a boy with a regular forty to fifty day cycle of psychotic behavior.

The figure shows a condensed form of the sleep and behavior records during the patient's eight months' stay in the Phipps Clinic. The chart shows three day averages of the daily records of manic, normal and depressed mood and behavior made routinely by the nurses. The patient entered the clinic during a period of manic excitement. In the course of the first ten days his chart showed that he was distractible, capricious, impulsive and restless; that he was industrious, cheerful and smiling, and that he played games. There was no depressive behavior or mood. After this period the chart showed a sharp reversal in behavior and mood. For a few days he was fairly normal and then became depressed, showing loss of initiative, brooding, preoccupation, sadness and fearfulness. After about ten days his behavior and mood again showed a sharp change. For a few days he was fairly normal and then became manic. The period of manic excitement lasted about thirty days. These cyclic changes repeated themselves with considerable regularity over the next seven months. The manic, normal and depressed phases varied somewhat in length from cycle to cycle, but in general the manic periods were about twice as long as the depressed phases. The intervening normal

his appetite was ravenous, and conspicuous acne of the face and the upper portion of the trunk developed. During the intervening periods of depression he was unresponsive, untidy and careless of his personal appearance and self depreciatory and exhibited both physical and mental slowing. He was motionless at times, with occasional suicidal threats and two actual attempts at self destruction. His appetite was poor to the point of his requiring spoon feeding at times. The onset of each depression was characterized by one to three days during which he complained of vague abdominal discomfort, without objective signs or symptoms.

The patient was transferred on Sept. 14, 1943 to another hospital for mental diseases. The diagnosis on discharge was "manic-depressive reaction in a 15 year old boy whose emotional maturity has lagged behind his physical and intellectual development." A note from the other institution five months, and again nine months, after the patient's transfer indicated that he continued to show variations in behavior, though they were not so regularly spaced as earlier in the illness.

6. Richter, C. P.: Two Day Cycles of Alternating Good and Bad Behavior in Psychotic Patients, Arch. Neurol. & Psychiat. **39**:587 (March) 1938.

On the basis of earlier work,[3b] it was thought that the forty day cycles might be indicative of disturbance of parathyroid activity. Accordingly, the calcium metabolism of the patient was followed rather closely. There was no pronounced variation in the calcium and phosphorus content or in the phosphatase activity of the blood during the different phases of activity. It is of interest that the calcium and phosphorus values remained nearly constant (calcium, 10.5 to 11.3 mg. and phosphorus, 3.8 to 4.8 mg. per hundred cubic centimeters), even when 30 Gm. of calcium lactate was added to an already high calcium diet. The phosphatase values showed relatively small variations but were consistently elevated (8 to 10.7 Bodansky units), presumably because of the patient's youthfulness, in spite of the fact that there was no detectable skeletal growth during the eight months that the patient was under observation. Serum proteins (estimated from refractive indexes) showed no changes in concentration.

The sodium content of the blood serum was determined three times, twice when the patient was depressed and once when he was manic. The values were definitely low during the depressed states and well within normal limits during the manic phase. It is regretted that, owing to wartime conditions, facilities were not available for further determinations of the sodium content or for the study of the excretion of 17-ketosteroids.

SUMMARY

In the case reported here unusually regular cycles of variation between depressed and highly manic behavior occurred in a 14 year old boy. The over-all cycle was between forty and fifty days, with transitions at first occurring with extreme abruptness (less than forty-eight hours in several instances) and later becoming increasingly gradual in onset. Attempts to associate these cycles with those of the endocrine glands were unsuccessful.

Phipps Psychiatric Clinic.

TAP AND THRUST RESPONSES IN PARKINSON'S DISEASE

ABRAHAM MYERSON, M.D., BOSTON

For about twenty years I have been eliciting certain ocular signs in cases of Parkinson's disease (paralysis agitans), and I believe that the observations merit a short report. I have called these signs the "tap reaction" and the "thrust response."

THE TAP REACTION

This response is obtained when the bridge of the nose and/or the forehead up to the hair line is tapped gently with the forefinger. In the positive reaction the eyes close spasmodically, and against the will of the patient, with each tap, and will close as often as the tap is repeated. In certain extreme positive responses the eyes close spasmodically, and after the first tap remain closed throughout the tapping and do not open again until it ceases.

In normal persons a few blinks are obtained when the forehead and the bridge of the nose are tapped in this manner. This reaction ceases after the first few taps, and the eyes remain open, despite the continuation of the tapping.

THE THRUST RESPONSE

When the forefinger is thrust toward, but does not reach, the eye of the normal person, a wink may take place, but this response ceases on repetition of the thrust and is not extreme. In the positive response, the eyes close spasmodically on the approach of the forefinger to the eye, and in typical instances the closure takes place with each thrust toward the eye. In some cases, as with the tap reaction, the closure becomes spasmodic and remains so for a prolonged period.

COMMENT

These reflex responses, which are probably largely of visual origin, since the tap does not evoke the reflex until it reaches a point where the finger or the hand of the examiner can be seen, are especially constant in cases of postencephalitic parkinsonism. They are prominent, though not universal, in cases of arteriosclerotic or senile Parkinson's disease. This might be expected, since postencephalitic Parkinson's disease is more frequently associated with disturbances of the extraocular muscles than is the case with the usual form of Parkinson's disease. With diseases of the basal ganglia of other types, these responses are present rather inconstantly. They are not present with the other organic diseases of the central nervous system.

It is curious that they are absent with all the functional nervous and mental disorders except catatonic dementia precox. In patients with this condition these responses occur with great frequency, but the incidence varies with the degree of the patient's catatonic state; that is, a patient will show these signs to a conspicuous degree when he is in the state of extreme passivity or retreat. When his condition is clinically improved or in remission, the signs disappear, and they may even disappear during the same examination, after having been evoked consistently. In other words, there is good evidence that in patients with this form of schizophrenia the involvement of the basal ganglia is not irreversible but symptomatic. It will be noted, too, that there is a superficial resemblance between the attitude, facial expression and general physical demeanor of a patient with severe Parkinson's disease, especially of the postencephalitic type, and the fixed postural and facial reactions of the catatonic state.

475 Commonwealth Avenue.

From the Division of Psychiatric Research, Boston State Hospital.

This study was aided by a grant from the Commonwealth of Massachusetts.

Obituaries

BERNARD SACHS, M.D.

1858-1944

Bernard Sachs, known to his family and intimate friends as "Barney," observed his eighty-sixth birthday on Jan. 2, 1944, in the characteristic spirit of optimism, trust and searching inquiry that was so familiar and stimulating to all who knew him. Several weeks later, on February 8, he died at his home in New York, a stoic to the end. He is survived by his wife, Mrs. Rosetta F. Sachs, and two daughters by his first marriage, Mrs. Jacob M. Plaut and Mrs. Nathan Straus.

Age touched Dr. Sachs but lightly as he graced the years with charm, lived the days with zest and gave meaning to life through work and accomplishment. He said himself—he was old, not aged. The spring left his step gradually, and the neatly cropped Van Dyke beard turned to gray slowly. His person and manner commanded respect. The impression was always one of dignity and decorum, which set him apart and brooked no easy familiarity.

When Sachs was born in Baltimore, in 1858, Lincoln had made his famous speech in acceptance of the Republican nomination to the Senate, and the Civil War was yet to be fought. He was one of red-haired twins who were added to a teacher's family, consisting of 3 sons and 1 daughter. The twin brother died of scarlet fever, at the age of 5 years. The other children were long lived and remained devoted to one another throughout life. The brothers achieved successful careers: Sam and Harry, in banking; Julius, in the field of education.

The parents, Joseph and Sophia Baer Sachs, were born in Germany and came to this country in 1847, settling first in Philadelphia and later in Baltimore. Joseph, a teacher by profession, belonged to that group of well trained, cultured, ambitious young Germans who were dissatisfied with the economic and social restrictions imposed on them in their own country; they came to America to enjoy its freedom and realize its opportunities. With such aspirations, Joseph Sachs resumed his teaching in Baltimore and, when his son Barney was about 2 years old, moved to New York and started a school of his own, which became a great success during and after the years of the Civil War.

It was natural that Sachs should receive his early instruction at home. It was a well ordered, liberal education, oriented in the humanities and supplemented by the strict discipline of good conduct. He flourished in this environment, and after the premature death of his father, came under the stimulating influence of his older brother Julius. The relationship between these two brothers was mutually inspiring. Julius imbued his young brother with a love and appreciation of art and music and helped mold the intellectual framework of his career. Barney was receptive and grateful. He frequently acknowledged in public his great debt to Julius for shaping his career and for bestowing on him the full benefit of his exceptionally wide culture.

Julius, who became an outstanding educator in his own right, personally prepared Barney for Harvard, which he entered in 1874. This choice of schools was auspicious, for here Sachs came under the forceful influence of William James, whose philosophy of realism and insistence on the immediate and actual took root in the soil of his early training. It was at this shrine of pragmatism that Sachs, without being wholly committed to the concept of expediency, learned to appreciate "the primacy of human experience." This direction of thought brought him back to the days when he and Julius attended Thomas Huxley's lectures at Cooper Union on the controversial topic of the day—Darwinism. The inquisitive young student soon discovered that James's pragmatism and Darwin's concept of the survival of the fittest were correlates of each other, or that the former stemmed, at least in part, from the latter. Sachs used this information to good purpose. He competed successfully for the Bowdoin prize with a dissertation entitled "A Comparison of the Fore and Hind Limbs of Vertebrates." When he was elected to the Phi Beta Kappa society and was asked to deliver the commencement address, he chose for his topic "Goethe as a Man of Science," in which he attempted to show that Goethe, in thought, was a forerunner of the nineteenth century evolutionists.

With the pattern of his career taking form, Sachs had the added good fortune to come in

closer contact with James and to get at first hand his personal interpretation of many perplexing problems. This came about when James, his vision failing, asked for a volunteer to read to him. Sachs offered his services. Significantly, the book to be read was Wundt's "Psychologie," which had just appeared in German and was rapidly becoming the psychologist's bible. Under this influence, Sachs became interested in philosophy and psychology and decided to devote himself to medicine, particularly to the diseases of the mind.

In 1878 he received his degree of Bachelor of Arts and planned to go to Europe for his medical training. At that time the Johns Hopkins, Cornell and New York University medical schools were not in existence, and the Columbia University College of Physicians and Surgeons and the Harvard Medical School were in their formative periods, and far from their present level of eminence. Sachs's choice fell on the new medical center which the Germans had erected at Strasbourg, after their conquest of Alsace, during the Franco-Prussian War. The medical faculty was exceptionally strong. It included the shining lights of German medicine: the anatomist Waldeyer, the physiologist Goltz, the internist Kussmaul, the pathologist von Recklinghausen and others of this illustrious group. Sachs was influenced in his medical outlook especially by Kussmaul, and referred to him as "that dear old master of medicine, who taught me to examine and treat the 'patient' and not the 'case.'" This was the basis of Sachs's bedside dictum throughout his career—that the art of medicine was just as important as the science. He himself never failed to live up to it.

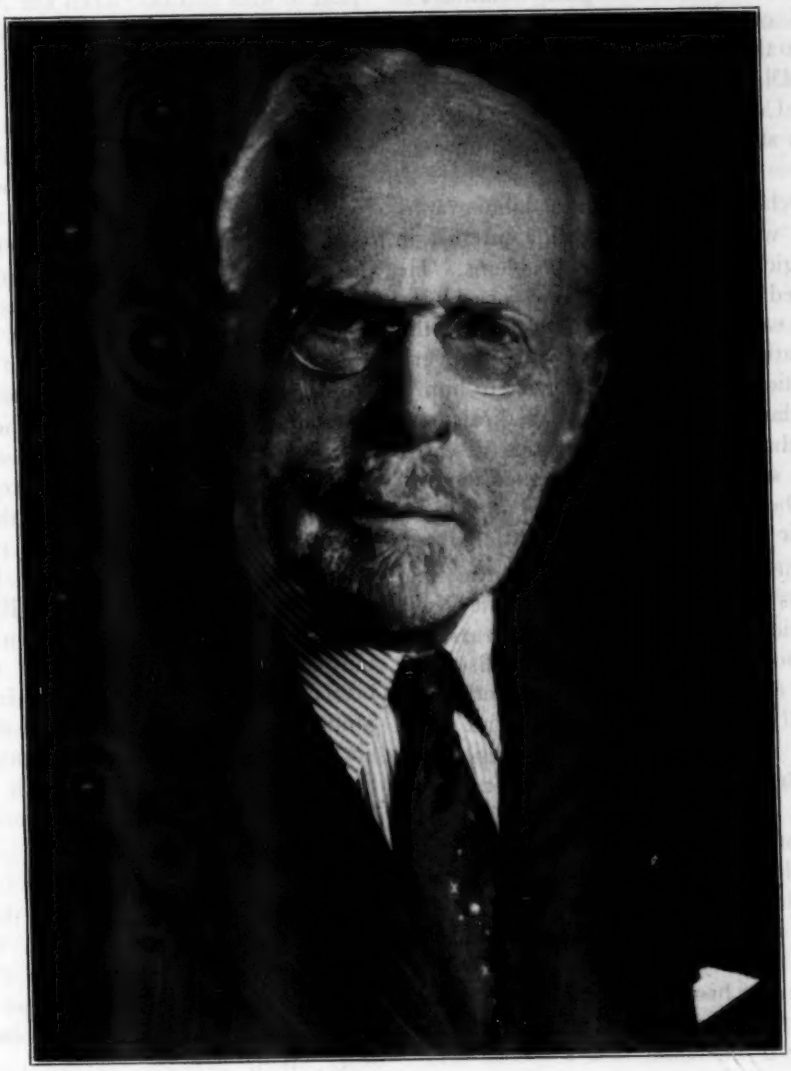
On June 6, 1882, Dr. Sachs received his medical diploma. Fifty years later, the faculty at Frankfort, which had taken over the University of Strasbourg, offered him an honorary degree. This he declined because he did "not care to be the recipient of any honor from a university system that completely ignores freedom of thought and freedom of speech, even in strictly scientific inquiries."

After graduation, Sachs, for two years, pursued intensive studies with Meynert, in Vienna; Hughlings Jackson, in London; Charcot, at Salpêtrière, in Paris, and Westphal, in Berlin. The great value of Meynert's neurologic laboratory lay in its intimate affiliation with the psychiatric clinic. Meynert was chief of both. It was largely owing to this early experience that Sachs became and remained always a believer in neuropsychiatry as a whole, not in neurology and psychiatry as separate practices. It is historically noteworthy that it was in Meynert's laboratory that he and Sigmund Freud first met. Only recently, in referring to this period, Sachs wrote: "None of us suspected Freud's future fame. He pegged away at anatomy, as we all did, and although his doctrines took him far afield, in his latest letter to me, written only a few months before his death, he acknowledged that he had never severed his relations with organic neurology. Evidently, his early training left a deep impression on him. It would be well if some of his closest followers had a similar training."

Sachs was anxious to get at Charcot's presentation of organic nervous diseases, but still more to learn his interpretation of hysteria and the use of hypnotism. He was soon convinced of the powerful influence of suggestion and was not astonished that Freud, who visited the Salpêtrière the next winter, was set thinking, although he "could never understand why Freud denied the effect of pure suggestion." The time spent at the Salpêtrière was both stimulating and refreshing. Sachs wrote of it later in glowing terms: "It was a great experience, after that dry, matter-of-fact teaching method of the German scientists, to revel in the more or less dramatic presentations, especially of clinical phenomena, by the great French master of science."

After devoting six years to preparation for practice, and with the teachings of Kussmaul, Meynert, Jackson and Charcot strongly impressed on him, Sachs felt ready for the fray. He returned to New York and, in May 1884, opened his office at 226 East Sixtieth Street. While giving full time to private practice, he was ever mindful of scientific work; in that first office he concealed a laboratory table behind a screen and, in the lull between patients, found time to cut, stain and study microscopic specimens. The early years of practice in New York brought Sachs good fortune. He assisted Seguin in his private practice and learned much from him in the way of neurologic diagnosis. It was then, in 1887, that he first encountered the disease that was to bear his name and reflect so brilliantly on his clinical acumen. The patient, an infant, presented the entity of arrested cerebral development and blindness to which Sachs later gave the name of amaurotic family idiocy. The accuracy of his observations has impressively withstood the test of time, which has served to add further luster to his name. This unusual distinction came to him at the age of 29, only five years after graduation from medical

school. This contribution to child neurology was by no means fortuitous; in a sense, it was derived from the interest of the Sachs family in the educational field. It is not surprising, therefore, that Dr. Sachs remained interested, for more than fifty years, in the domain of nervous and mental disorders of children. His efforts along these lines were rewarded when the Friedsam Foundation established the Child Neurology Research Fund under his direction. Sachs regarded this achievement as the "crowning glory" of his career.



BERNARD SACHS, M.D.
1858-1944

The year 1887 was a banner one for young Barney, for he not only made his medical mark but married Bettina R. Stein, of Frankfort on the Main, a woman of staunch character and keen intellect, with a fine critique and love of the classics. In art, music and literature she was a woman of discrimination. For fifty-three years, until she died in 1940, she followed her husband's career with pride and understanding.

Sachs contributed prolifically to the literature of medicine. His first literary undertaking was to translate into English Meynert's "Psychiatry." This was no easy task. The thought and language were involved and difficult to unravel. But having set out to do the job, he did it. Edinger was so impressed with the translation that when he met Sachs in the summer of 1888, he said to him: "You have managed to translate Meynert into English; it is difficult enough for us to understand him in German." It is well

to remember that the Babinski reflex and the Wassermann reaction were still unknown when Sachs published the papers entitled "Ueber den Einfluss des Rückenmarks auf die Harnsekretion" in 1881; "On the Use of the Galvanometer," in 1882, and "Tumors of the Spinal Cord" and "Arrested Cerebral Development, with Special Reference to Its Cortical Pathology," in 1886, and, in subsequent years, articles on the cerebral palsies in infants and the surgical treatment of epilepsy and of trigeminal neuralgia. It was fifty years ago that he wrote his book "A Treatise on Nervous Diseases of Children" (New York, W. Wood & Co., 1895). It was acknowledged to be the first standard text of its kind published in America.

His research is recorded in a bibliography of 194 titles, which reveal his wide interest in both neurologic and psychiatric problems. He always insisted that neurology and psychiatry supplemented each other and stressed further the important relation that neurology bore to every branch of medical and surgical science; to him it was "the fundamental specialty of medical art." He insisted that mental and nervous diseases should not be studied apart and warned against allowing psychology to advance too far ahead of the anatomic and physiologic foundations.

Realizing the great importance of a teaching position, Sachs affiliated himself with the New York Polyclinic, where, within a few years, he became professor of nervous and mental diseases, at the ripe old age of 30. He made his influence felt in many of the hospitals in New York city. At one time or another he held important positions at Bellevue Hospital, the Montefiore Home and the Mount Sinai Hospital, where, in 1900, he organized a full neurologic service, the first of its kind to be established in any hospital for voluntary admissions in the city. The service took up a large part of his time for almost a quarter of a century, until he was retired in 1924, on account of his age. Later, in 1942, the Mount Sinai Hospital, in recognition of his sixty years of service to medicine, held a special ceremony and commemorated the occasion with the publication of an anniversary volume, in which may be found the important dates and events of his life, as well as the scientific tributes of his colleagues.

The career which earned Sachs the title of dean of American neurology was replete with honors and associations attesting to his eminence in the neuropsychiatric world. At the age of 36 he was elected president of the American Neurological Association, a distinction which was again conferred on him at the age of 74. The year before this he had been unanimously chosen by the delegates of many nations as the president of the First International Neurological Congress, to be held in Berne, Switzerland, in 1931. His election to this position reflected his wide personal and popular acquaintance with the neurologists of the world, as well as the high esteem in which they held him. Further tribute was paid to him in 1933, when the New York Academy of Medicine recognized his leadership in American neurology by electing him to its presidency.

Of Dr. Sachs it can truly be said, with Terence: "Homo sum, humani nil a me alienum puto," for he was a man of wide and varied interests. Through them he made friends with men of distinction in various fields. One friend in particular, Benjamin Altman, played an important part in his life. Sachs attributed this friendship to a common interest in art. As Altman assembled his collection of porcelains and masterpieces, which now constitute one of the outstanding possessions of the Metropolitan Museum of Art, Sachs followed each addition with great interest, and so acquired excellent judgment as to the merits of the great works. So much so that it was on his recommendation that the famous portrait of Philip IV, by Velásquez, was purchased in 1911. The garland of the art critic rested jauntily and pleasingly, if not too securely, on the physician's brow. In appreciation of his friendship, Benjamin Altman made him one of the executors of his will and a trustee of the Altman Foundation. Sachs kept in close touch with the officers of B. Altman & Company for more than thirty years.

To Sachs, the next important interest was the Charaka Club, to which he gave the name. Here, the founders—Bernard Sachs, Charles Dana, Frederick Peterson and Joseph Collins—met to discuss subjects of cultural rather than of medical interest. Later they were joined by William Osler, Weir Mitchell, Arpad Gerster, Harvey Cushing and many other physicians of eminence. Medical discussions were taboo. The members explored the fields of art and philosophy; they presented original poems, short stories, drawings and etchings. This tradition has continued, and at Sachs's last visit to the club, in 1943, when he reflected on the early days and recalled golden memories, he expressed pride and satisfaction that the members were carrying on in the spirit of the founders. For forty-five years he had been most faithful in his attendance at the meet-

ings, at which he was a scholar among scholars in medicine.

As Terence's aphorism implies, Sachs was not only a good physician, and a man of art and letters, but a good citizen. As chairman of the Committee on Outdoor Cleanliness, established by the Academy of Medicine, he took great pride in the city and was frequently twitted for his persistent efforts to force the New York authorities to keep the city streets clean in the interest of public health. This was really a one man crusade, but it succeeded, for it stirred up the department of sanitation to improve its methods and equipment.

The years rolled on. Sachs took his holidays, in the days of world amity, in Switzerland, and occasionally in Scotland. Each year he tested his ability to climb the Swiss mountains. Mountain climbing and walking were his chief sports. Occasionally he played golf. At one time, when the sand traps of California were too much even for his stalwart spirit, he proclaimed that golf was not a game but a lesson in humility.

When he was just 50 years of age, and well known through his scientific achievements, he put himself to the test to determine whether he was still receptive to knowledge and capable of taking on entirely new lines of work. The Wassermann reaction had just been made known to the world. Sachs determined to go directly to Wassermann's laboratory and learn the method at headquarters. When he caught on readily, he gained new confidence in himself. However, despite this personal achievement, he always insisted that clinical diagnosis should not depend too largely on laboratory tests, and pointed out: "To those who may be inclined to have a slight sneer for the clinician and think him inferior to the laboratory worker, let me say, as I have said elsewhere: all true scientific research in medicine stems from the bedside."

Sachs viewed life with equanimity. Life was good to him, gave him no cause for envy. His faith was created by his conscience and sustained by an ethic of good and the confidence of his heart. He likewise adhered to the principle of Heraclitus: "Man's character is his fate." From this principle Sachs derived his credo of hard work, the satisfaction of a job well done and the great sense of responsibility to himself and others. In his daily life, hope played a greater part than fear. He was an optimist and believed that everything in nature was ordered for the best and that one special principle—hard work—was essential to produce the highest good. His was a reality of the present, in which personality was the important and determining factor in life. It alone endured and flowed through time.

The Sachs attributes of vitality, awareness, courage and intelligence will be long remembered. He had great force of mind and body—it was undoubtedly this quality which gave him the power for hard work and stimulated and sustained his interest in the world about: whether it was medicine, culture, the theater, or civic duty. This great urge endured almost to the end, for only a few weeks before he died, he was still mapping out a plan of research in heredity along biochemical lines and reading Page's book on the biochemistry of the brain. He fortified this vitality against the time when it might ebb by keeping in touch with younger men and seeking their opinions. It is not surprising, therefore, that he, in turn, was sought by the younger men, who will always remember him with affection and gratitude.

Sachs was an intelligent man—interested more in general propositions than particular fact. He thought clearly and did not linger in confusion, certainly not for long. He had a solicitous care for order and form but never substituted the form of the symbol for the spirit of its meaning, nor did he ever confuse the two. He had knowledge and, even more important, the aptitude for acquiring it. Out of this receptivity grew a searching curiosity which contributed to a flexibility of mind that was his distinguishing characteristic to the last. Yet he was a man of strong convictions, and his convictions had force and effect.

Sachs saw and helped neurology in America pass from adolescence into vigorous manhood. Those who listened to his forceful convictions on so many occasions and enjoyed his freshness and humor and admired the strength of his personality are apt to forget that he belonged to the heroic age of neurology and psychiatry. When looked back on, this period takes on special meaning, and although time has somewhat blurred the outline, it has brought the labors of this epoch to fruition. The earlier, and necessarily precise, studies of the neural architecture, when structure was being analyzed and categories established, laid the groundwork for the later appreciation of the function of the nervous system. Sachs scaled the heights of this era but did not permit his Mount Olympus to become an ivory tower. He looked beyond and joined with the next generation. He brought with him the wisdom of his age to give maturity to the present and lend promise to the future. He himself was the fulfilment of the promise of that period.

In this chronicle, the deeds, even more than the years, measure the man. In the numerous contributions to neurology and psychiatry, the spirit of the dictum which Sachs prescribed for one's remaining young in spirit is evident: "The joy of work is the joy of life." In this survey of a full life and its contributions to mankind, the laureled physician stands out, for his very presence in medicine gave it dignity.

I choose to think of Dr. Sachs now as I did on the occasion of his eighty-fifth anniversary, when I wrote: "The flow of production which began in 1881 has helped to cultivate many fields in neurology. The stream of thought has been fresh and clear, the current strong; strong enough to clear away the underbrush and cut new paths. Obstacles have served only to emphasize the strength of the current, as it either swept them aside or carried them along in the wake of its course."

"The biographic milestones along the banks mark well the progress of the stream, and those of us who have been so fortunate as to sit by the banks have found the stream deep, the view broad and the waters not without sparkle."

LOUIS HAUSMAN, M.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

ACETYLCHOLINE LEVEL OF RAT CEREBRAL CORTEX UNDER CONDITIONS OF ANOXIA AND HYPOGLYCEMIA. JOHN H. WELSH, J. Neurophysiol. **6**:329 (Sept.-Nov.) 1943.

Welsh compared three methods for the extraction of acetylcholine from the cerebral cortex of the rat: (1) the trichloroacetic method, (2) the dialysis method and (3) a rapid method of extraction in cold isotonic solution of three chlorides (Ringer's solution). The last method was found to be the most satisfactory. The methods of assay employed (1) a leech muscle preparation, (2) the isolated, physostigminized frog heart and (3) the isolated heart of the mollusc Venus merceneria. Rats subjected to low atmospheric pressure for one to two hours showed a decrease in the free and total acetylcholine content of the cortex of approximately one third to one half. This decrease induced by low atmospheric pressures could be prevented by the prior administration of prostigmine bromide. Insulin hypoglycemia resulted in a greater decrease of free acetylcholine than did anoxia. Welsh suggests that the decrease in free acetylcholine under conditions of anoxia and hypoglycemia may explain the decrease in excitability of the cortex under these conditions.

FORSTER, Philadelphia.

EFFECTS ON EEG OF CHRONIC LESIONS OF BASAL GANGLIA, THALAMUS AND HYPOTHALAMUS OF MONKEYS. MARGARET A. KENNARD, J. Neurophysiol. **6**:405 (Sept.-Nov.) 1943.

Kennard studied the effects of chronic lesions of the basal ganglia, thalamus and hypothalamus on the electroencephalograms of 52 monkeys. While lesions restricted to the cortex did not alter the electroencephalographic pattern, lesions of the basal ganglia caused changes. Permanent alterations were produced by large lesions of the basal ganglia or of the basal ganglia and the cortex. Clinical seizures and electroencephalographic patterns of seizure type frequently occurred after lesions of the basal ganglia. The electroencephalographic changes following lesions of the basal ganglia could be correlated with the functional changes. Lesions of the thalamus caused marked slowing of rate, irregularity of pattern and the appearance of high, slow, rounded waves at frequent intervals. Hypothalamic lesions produced notable slowing with decreased amplitude, so that with extensive hypothalamic lesions practically no pattern of potentials remained. Kennard suggests that the post-traumatic changes in the electroencephalograms of both man and monkey may be directly related to changes within the basal ganglia.

FORSTER, Philadelphia.

NATURE OF PARESIS FOLLOWING LATERAL CORTICO-SPINAL SECTION IN MONKEYS. B. W. CANNON, CAPTAIN L. E. BEATON and CAPTAIN S. W. RANSON JR., J. Neurophysiol. **6**:425 (Sept.-Nov.) 1943.

Cannon, Beaton and Ranson studied the effects of dorsolateral chordotomies in the cervical and thoracic regions of the spinal cord in 9 Macaca mulatta monkeys. Interruption of the lateral corticospinal tract resulted in paresis more prominent in the lower than in the upper extremity and more pronounced distally than proximally. This paresis was characterized by hypotonicity, hypoactive reflexes and absence of clonus. The authors conclude that in the lateral corticospinal tract of the monkey there are no descending inhibitory pathways interruption of which results in spasticity.

FORSTER, Philadelphia.

REMOVAL OF ACETYLCHOLINE BY CHOLINESTERASE INJECTIONS AND THE EFFECT THEREOF ON NERVE IMPULSE TRANSMISSION. BRUNO MENDEL and ROSEMARY D. HAWKINS, J. Neurophysiol. **6**:431 (Sept.-Nov.) 1943.

Mendel and Hawkins injected purified cholinesterase intravenously into animals and thus prevented the chromodacryorhetic effect of injected acetylcholine. By the injection of the cholinesterase preparations the authors demonstrated that acetylcholine plays an essential role in the transmission of impulses to the sphincter of the pupil, since the direct light reflex could be totally or partially abolished by the injection of a cholinesterase preparation.

FORSTER, Philadelphia.

AFFERENT AREAS IN THE BRAIN OF UNGULATES. E. D. ADRIAN, Brain **66**:89, 1943.

Adrian mapped out the areas of the cerebral cortex receiving afferent discharges from peripheral receptors in goats, sheep, pigs and horses. The electrical activity was recorded from the surface of the cortex and from deeper layers while tactile and pressor receptors were stimulated. In the goat and sheep the chief supply of the cortical afferent area was derived from the ipsilateral upper and lower limbs, while occasionally discharges from the contralateral limbs could be obtained. In the pig the entire cortical receiving area seemed to be taken up with the representation of the contralateral half of the snout. The proportion of this area in the pig suggests that the tactile discrimination in the pig's snout should be at least as great as that in the human hand. The relatively poor representation of the limbs and trunks in these animals seems to be related to their mode of feeding and to the use of the extremities solely for locomotion and posture. In the horse, discharges reach the cortex from the contralateral nostril and limbs. Adrian suggests that the ipsilateral representation of the lips in sheep and goats may be due to the dominance of smell rather than of vision, while in the horse and pig the receptors around the nostril are used for tactile impressions and hence representation is contralateral, to correspond with vision.

FORSTER, Philadelphia.

Neuropathology

ANATOMIC AND PATHOLOGIC CONSIDERATIONS IN CONVULSIVE DISORDER. RAYMOND WAGGONER, K. LOWENBERG and ROGER W. HOWELL, Am. J. Psychiat. **99**:676 (March) 1943.

Waggoner, Lowenberg and Howell discuss the occurrence of convulsions in cases of meningeal infection, cerebral degeneration and occlusion of cerebral vessels.

However, they point out that the pathologic changes do not explain the convulsions and that pathologic processes may exist in the absence of convulsions, while in cases of so-called idiopathic epilepsy the converse is true. The authors are of the opinion that the occurrence of convulsions in patients with extensive cerebral lesions is linked with a latent convulsive diathesis.

FORSTER, Philadelphia.

RUPTURE OF ANEURYSM OF CIRCLE OF WILLIS: RELATIONSHIP BETWEEN INTRAOCULAR AND INTRACRANIAL HEMORRHAGE. JAMES N. GREEAR JR., Arch. Ophth. **30**:312 (Sept.) 1943.

Hale-White made the earliest observation, in 1895, on intraocular hemorrhage associated with intracranial hemorrhage which had extended into the intervaginal spaces of the optic nerve.

In the case which Greear reports postmortem examination was made in exacting detail. Serial sections were made from the posterior half of the globe to a point behind the entrance of the central retinal vessel into the optic nerve. Other sections were made through the nerve at the optic foramen. Sections also were taken through the aneurysm itself. The histopathologic studies revealed pronounced dilatation of the central vein intraocularly, with collapse of the vein in the subarachnoid space about the optic nerve. There was no suggestion that the hemorrhage had entered the eye from the meningeal spaces about the nerve. Greear believes that the intraocular hemorrhages were the result of sudden and severe interference with the return of venous flow of blood from the retina itself, and not the extension of intracranial hemorrhage, as first postulated by Hale-White.

SPAETH, Philadelphia.

THE CENTRAL NERVOUS SYSTEM IN TETANUS. A. B. BAKER, J. Neuropath. & Exper. Neurol. **1**:394 (Oct.) 1942.

Baker reviews the literature concerned with the pathologic lesions of the central nervous system associated with tetanus and records his own observations on 12 human brains. Grossly, some of the brains appeared entirely normal, while others showed mild congestion or petechial hemorrhages, some of which had fused to produce softened areas. Microscopic examination revealed patchy areas of damaged nerve cells scattered through the cerebral hemispheres, the brain stem and the spinal cord. The changes in the nerve cells varied from mild swelling and chromatolysis to extreme ballooning, severe loss of chromatin and pyknosis of the nuclei. If the illness had lasted more than five days, perivascular areas of demyelination and astrocytic gliosis appeared. Such lesions were widely disseminated throughout the neuraxis, but predominated within the cerebral hemispheres and increased with the severity of the illness. The author concluded that the changes in the nerve cells were the first to appear and might be observed as early as the third day of the illness. There seemed to be a tendency for the earliest and most extensive changes to be in the vicinity of blood vessels of moderate size. Within the spinal cord, cellular alterations were usually limited to the anterior horns but showed no tendency to select specific segments of the cord. The nuclei of the cranial nerves, for the most part, were not involved. However, in patients dying of respiratory failure after an eight day illness, the cells of the dorsal nucleus of the vagus nerve showed severe toxic changes.

The author believes that the widespread scattering of all lesions and their consistent perivascular distribution favor the theory of the hematogenous spread of tetanus toxin.

CAMPBELL, New York.

MULTIPLE TUMORS OF THE BRAIN OF DIVERSE ORIGIN. PAUL G. MYERSON, J. Neuropath. & Exper. Neurol. **1**:406 (Oct.) 1942.

Myerson reports on the clinical and neuropathologic observations in a case in which there were six tumors in the right side of the brain, 3 of which were meningiomas and 3 primarily gliogenous.

The patient, a man aged 60, with a six weeks' history of symptoms and neurologic signs indicating an infiltrating tumor in the right frontotemporoparietal region, died eight days after his admission to the hospital, soon after bilateral trephination and puncture of the left ventricle. Necropsy revealed that the cerebral convolutions were broadened and the sulci narrowed. There were several irregular, discolored, hard nodules in the frontal and parietal cortex on the right side. The right occipital lobe was conspicuously softened and discolored.

On section, six distinct lesions were observed in the right side of the brain. Two, in the second frontal convolution, showed the histologic characteristic of meningioma and contained no glial elements; a third, cystic in appearance, was present in the cortex of the right occipital lobe, near its junction with the parietal lobe. This had many features in common with the former tumors and contained no glia elements. The three remaining tumors were situated, respectively, in the centrum semiovale of the right parietal lobe, in the lower half of the right occipital lobe throughout its entire length, and extending into the posterior portion of the right temporal lobe, and in the dorsal two thirds of the right thalamus, extending into the midbrain. Sections of these three tumors stained by the gold chloride–mercury bichloride method revealed that most of the cells were gliogenous.

The author subscribes to the Cohnheim-Ribbert theory of embryonal rests and applies it to tumors of the brain. He speculates that "whatever causes these rests to become neoplastic also acts on cells of different development, but on much more primitive cells and cells which are fewer generations removed from their common origin."

CAMPBELL, New York.

Diseases of the Brain

DIPLOPIA IN NARCOLEPSY. MAX LEVIN, Arch. Ophth. **29**:942 (June) 1943.

Levin discusses the problem of diplopia in narcolepsy. The diplopia, just as in the case of paralysis, may occur just before the patient falls asleep or just after he awakens, and, like paralysis, it may be present as an isolated symptom and without apparent reason. Diplopia has also been seen only when reading is attempted. In addition, it may appear when one is attempting to ward off an impending attack of sleep. The author's summary suggests that narcolepsy results from a disturbance in the cerebral cortex or elsewhere which renders the cortex unduly exhaustible or "inhibitable," the attacks of sleep arising from inhibition of the whole cortex and the attacks of flaccid paralysis from inhibition of the motor cortex alone (plus, probably, certain subcortical motor centers). Levin calls attention to the frequency of attacks of diplopia with narcolepsy

and suggests that they arise from transitory inhibition of a cortical mechanism for binocular vision.

SPAETH, Philadelphia.

DYSMORPHOPSIA DURING THE COURSE OF SULFANILAMIDE THERAPY. NATHAN SAVITSKY and HYMAN WEITZEN, J. Nerv. & Ment. Dis. **98**:130 (Aug.) 1943.

Neuropsychiatric complications as a result of sulfonamide therapy include polyneuritis, transverse lesions of the cord, amyotrophic lateral sclerosis, encephalomyelitis, transient psychoses, motor aphasia and agraphia, optic neuritis and transient myopia. Savitsky and Weitzen report the case of a housewife aged 25 who, after receiving a total of 8.6 Gm. of sulfanilamide, complained of blurred vision and strange visual experiences. For two days objects appeared distorted to her. Thus, her own fingers appeared short and pudgy, and at times they seemed to show an angular distortion. Objects in the ward looked unusually thin and had curvilinear distortions, such as are seen in trick mirrors. Neurologic examination gave entirely negative results, and there was no evidence of aphasia, agnosia or apraxia. In two days the experiences ceased. The authors believe that the metamorphopsia must be regarded as cerebral in origin, and due to the sulfanilamide.

CHODOFF, Langley Field, Va.

INDIRECT INJURIES OF THE OPTIC NERVE. J. W. ALDEN TURNER, Brain **66**:140, 1943.

Turner reports 46 cases of indirect injury to the optic nerve as the result of head injury. Almost invariably the site of injury was to the frontal region. In the majority of cases the head injury was severe, as judged by the duration of unconsciousness, but in some instances loss of consciousness was of short duration and in 1 case it was absent. The effect on the optic nerve was immediate. Often at the onset there was complete blindness, improvement of vision beginning by the fourth day if useful vision was to be recovered. Maximum recovery occurred by the fourth week, and the improvement was almost invariably maintained. In all instances the injury of the optic nerve was unilateral. Visual acuity varied from complete blindness to normal vision. Visual field defects consisted of scotoma (8 cases) or peripheral sector defects (19 cases). In the early stages no changes occurred in the optic disks. In cases in which injury produced complete blindness pallor was first noticeable toward the end of the third week and then rapidly progressed. In cases of severe injury the pupils were dilated, and on the affected side there was absence of the direct light reflex with a maintained consensual light reflex. In 1 instance a traumatic Argyll Robertson pupil was present.

Turner advances the hypothesis that the indirect injuries are the result of sudden jarring of the optic nerve with violent impingement against the bony wall of the canal, so that rupture of the small vessels in the septums of the nerve and consequent thrombosis and softening are produced.

FORSTER, Philadelphia.

Diseases of the Spinal Cord

HERNIATION OF THE NUCLEUS PULPOSUS AS A COMPLICATION OF PRE-EXISTING LOW BACK INSTABILITY. EDWIN M. DEERY, Surg., Gynec. & Obst. **77**:79 (July) 1943.

Deery divides cases of herniated nucleus pulposus into two groups: the one composed of uncomplicated cases, in which the complaint is predominantly that of sciatic neuritis, with a minimum of "low back pain" and no outstanding previous history of "back trouble," and the other, of cases of herniated disk which complicates preexisting instability of the lower part of the back. In the latter group, with which this report is concerned, there are a long history of pain in the lower part of the back and relatively recent and predominant sciatic pain. It is in cases of this type that the combined operation of removal of the herniated nucleus pulposus and fusion of the lumbosacral portion of the spine is required. The presence of a herniated disk, as well as its level, is revealed by a careful neurologic examination. The history of sciatic pain is held to be important for diagnosis, but Deery does not believe it is specific for herniated disk. Objectively, muscular atrophy is commonly observed, the gluteal muscle, in addition to the thigh and calf, on the affected side being often atrophic. Sensory changes are a more reliable guide to the level of the lesion than are motor signs, since in almost all patients the ankle jerk is decreased or absent. The location of the herniated disk is not always at the fourth lumbar interspace. Sensory changes along the outer side of the lower portion of the leg and the ankle and foot generally indicate that the herniated nucleus is at the lumbosacral interspace. If, in addition, there are sensory losses on the inner side of the foot, from toe to heel, the herniation will be found in the fourth lumbar interspace. A narrowed intervertebral space seen in roentgenograms is not a reliable guide either to the presence or to the level of a herniated nucleus.

Injection of iodized poppyseed oil has not been found necessary for diagnosis of herniated nucleus pulposus. A positive result in such a study is excellent proof of the existence of a protruded disk; a negative result is not reliable proof of its absence. Air myelography, after a fair trial, was given up as being unsatisfactory.

When the diagnosis both of a surgically unstable joint and of a herniated nucleus pulposus is made, fusion and removal of the disk are carried out at the same time. If protrusion of the disk is suspected but the diagnosis is not definite, exploration for it is undertaken at the time of the fusion operation. A surprising number of such protrusions have been revealed in this way. The method employed is the interlaminar approach, with little or no removal of bone. A herniated nucleus pulposus may be one of three types: the most common is a small, round or oval mass still covered by the overlying lateral portion of the posterior longitudinal ligament; the second is the herniated nucleus that has forced its way through the posterior longitudinal ligament, and the third, the so-called hidden disk, a small, almost flat, lesion, with characteristic rubbery resistance, which apparently varies in size with changes in the position of the patient. Removal of the third type relieves pain. After removal of the disk the thickened ligamentum flavum in the region of the foramen is curetted away and a probe passed out along the nerve to be certain that there is no compression of the root as it passes through the foramen.

Fusion relieves the complaints produced by the unstable condition of the back but does not relieve sciatic neuralgia due to a herniated intervertebral disk.

SHENKIN, Philadelphia.

PROTRUDED INTERVERTEBRAL DISKS. J. GRAFTON LOVE and MAURICE N. WALSH, Surg., Gynec. & Obst. **77**:497 (Nov.) 1943.

Love and Walsh believe that protruded intervertebral disk is a better term than herniated nucleus pulposus,

since their pathologic studies have shown that the protruded portion of the disk practically always consists of nuclear and annular material. Protruded disk has come to be looked on as the result of trauma, most often associated with the lifting of unusually heavy objects. The symptoms may be abrupt, or they may be gradual in onset.

In the diagnosis of this lesion, in the lumbar region, the history is of cardinal importance. The important points to be determined are the relation of onset to trauma, the presence or absence of backache prior to the sciatic pain and the effects of coughing or straining on the pain. Pain is often severe at night, and loss of weight due to pain may be extreme.

In a series of 285 cases a positive Lasègue sign was present in 81 per cent, and alteration of the achilles reflex and tenderness of the sciatic nerve each were noted in 60 per cent. Sensory loss and muscular paresis were each noted in 22 per cent of cases. Neurologic examination gave negative results in 6 per cent and negative results except for a positive Lasègue sign or sciatic tenderness in 15 per cent. A lumbar puncture to rule out tumor of the spinal cord should be performed in every case.

The authors believe that in only a small percentage of the cases of backache encountered in general practice is the pain due to protruded disk, since in the majority of such cases the condition responds to conservative therapy. In 13 per cent of 5,500 cases of backache occurring in one year in the section of orthopedics of the Mayo Clinic a protruded disk was later proved to be the cause.

Subarachnoid block is produced only by the largest lesions, which are capable of causing gross neurologic signs by pressure on the cord or the cauda equina. In the presence of "low back pain" and sciatic pain, subarachnoid block, a high protein content of the spinal fluid or a xanthrochromic fluid, a tumor of the spinal cord should be suspected.

Radiopaque oil is only seldom used because clinical diagnosis is just as accurate and medicolegal complications might follow its use. Air myelography is considerably less accurate in the diagnosis of protruded disk than is either clinical examination or oil myelography. It is used almost routinely, however, as an adjunct in diagnosis to reveal multiple protruded disks and to exclude an unsuspected neoplasm. After operation patients are mobilized as early as the fourth day but are kept in the hospital until the twelfth day. A three month period of convalescence is then advised.

Fusion following removal of the disk is advised in cases in which there exist (1) associated spondylolisthesis, (2) a long history of backache preceding the sciatica or (3) definite roentgenographic evidence of disease of the vertebrae.

Fusion is not advised in cases of patients over 55, since the prolongation of the stay in the hospital definitely increases the risk. The mortality for the operative removal of protruded disk is less than 0.25 per cent. Complete relief from symptoms should occur in 80 per cent of cases, and the incidence of recurrence of protruded disks in the lumbar area has been 2 per cent. All patients with borderline conditions are advised to submit to from three to six months of constant orthopedic treatment.

SHENKIN, Philadelphia.

STUDIES OF NEUROMUSCULAR DISORDERS: THE MYOGRAM, BLOOD CHOLINESTERASE AND EFFECTS OF PROSTIGMINE IN MYASTHENIA GRAVIS AND PROGRESSIVE MUSCULAR ATROPHY. GUY ODOM, COLIN K. RUSSELL and DONALD MCEACHERN, Brain **66**:1 (March) 1943.

Odom, Russell and McEachern made neuromuscular studies in 11 cases of myasthenia gravis and in 6 cases of progressive muscular atrophy. In 3 of the latter sufficient evidence of involvement of the corticospinal tract was present to permit their classification as cases of amyotrophic lateral sclerosis. Normal persons respond with a sustained muscular contraction to any rate of stimulation between 34 and 840 shocks. In 9 of the 11 cases of myasthenia gravis a characteristic abnormality was noted in the myograms. This consisted in failure to maintain the contraction after stimulation at rates above 90 per second. The failure was most conspicuous at rates between 90 and 180 shocks per second. In addition, in cases of myasthenia the height of contraction was poor, higher voltages being necessary to obtain good records. In 2 cases the abnormal myogram was of definite diagnostic help in study of the effects of treatment. Prostigmine restored the myogram of myasthenic patients to normal in about forty-five minutes after intramuscular injection. Injection of prostigmine methylsulfate into the brachial artery of a limb the venous return of which was obstructed resulted in a return of the myogram to normal within one minute without production of any improvement in the myogram of the opposite limb. Release, then, of the venous return of the limb into which the drug was injected was followed in several minutes by generalized improvement. One hour after the intra-arterial injection the limb used for injection was still normal, while the limb on the opposite side never became quite normal. The cholinesterase content of the blood, at the same time, had risen above the level existing prior to the injection of prostigmine, an indication that the persisting effect of the drug on the muscles of the limb into which the injection was made and the level of cholinesterase in the circulating blood are not essential factors.

The variations in the level of cholinesterase in the blood of the myasthenic patient over a given period are no greater than those in normal persons, and the level falls within the wide range of normal. Prostigmine causes a pronounced and constant fall of cholinesterase in the serum of normal persons, as well as in that of myasthenic patients.

The authors conclude that the beneficial action of prostigmine is peripheral and that the reduction of muscle cholinesterase is the essential factor, since myasthenic patients unresponsive to intramuscular injection of prostigmine respond with a normal myogram after intra-arterial injection.

In cases of progressive muscular atrophy the myograms were normal, but many irregular twitches, due to fasciculations appeared. The cholinesterase contents of serum and of whole blood were within normal limits in all cases of this condition. Prostigmine caused a reduction of blood cholinesterase as usual, and fasciculations appeared, or were greatly intensified, during the time of action of the drug.

In 3 cases in which spontaneous fasciculations were present in the anterior tibial muscle, the common peroneal nerve was completely blocked with 1 per cent procaine hydrochloride; nevertheless, fasciculations in this muscle persisted with the same intensity. Intramuscular injection of prostigmine increased fasciculations generally, including the muscles the nerve supply of which was blocked. The authors conclude that the fasciculations are of peripheral origin, and are not due to disordered impulses arising in the anterior horn cells. In 2 other cases, in which fasciculations were elicited from the anterior tibial muscle by posturing of the limb, nerve block caused fasciculations to disappear. This was attributed to the fact that the mechanism of fasciculations in this group was due to toxic impulses descending from the anterior horn cells when the limb was postured. Patients with progressive muscular atrophy showed fasciculations after even small doses of prostigmine methylsulfate (0.5 mg.). Normal persons had fasciculations only after much larger doses. Myasthenic patients did not give this response even after doses of 2.5 mg.

The authors discuss the possible defects in neuromuscular transmission which may be responsible for myasthenia gravis, namely, (1) excessive activity of blood cholinesterase; (2) overactivity of tissue esterase at the neuromuscular junction; (3) liberation of abnormally small amounts of acetylcholine at the neuromuscular junction, and (4) existence of a curare-like substance in this disease.

SHENKIN, Philadelphia.

Treatment, Neurosurgery

THE NEUROLOGICAL AND ENDOCRINE ASPECTS OF ATROPHIC ARTHRITIS (DEFORMANS). SIMON STONE, J. Nerv. & Ment. Dis. **97**:638 (June) 1943.

Stone considers the possibility that a nutritional deficiency engrafted on an inherited neuroendocrine instability may be an etiologic factor in some cases of atrophic arthritis. In view of the demonstrated relation of lack of vitamin E to various types of neuromuscular disturbances, the author was prompted to try the effect of this vitamin on patients with atrophic arthritis not caused by infection. A group of 22 patients with various stages of the disease, ranging in age from 13 to 58 years, were treated for periods ranging from six to eighteen months. Vitamin E in the form of wheat germ oil, in doses of 4 to 8 cc. daily, was administered in combination with the vitamin B complex. Artificial fever, orthopedic procedures, inductothermy and administration of iron and liver preparations were also used in some cases. Of the 8 patients with less advanced disease, varying degrees of improvement were apparent in 6. Eleven of the 14 patients with more advanced disease were decidedly benefited, so that 80 per cent of the entire series was helped by the treatment.

The author believes that administration of vitamin E in cases of this disease has produced reduction or disappearance of periarticular exudate, and in some instances regeneration of atrophied muscle. This may be due to the gonadotropic, as well as to the neurotropic and myotropic, effects of the vitamin. It is also possible that in certain cases atrophic arthritis is etiologically related to amyotrophic lateral sclerosis in women. The results of the treatment were better in women than in men, especially when small doses of stilbestrol were added. No effects were noted in cases with hypertrophic arthritis.

CHODOFF, Langley Field, Va.

CATAPLEXY AND ITS TREATMENT. JOHN B. DYNES, J. Nerv. & Ment. Dis. **98**:48 (July) 1943.

Because of the resemblance of cataplexy to periodic familial paralysis, Dynes suggests that faulty potassium metabolism may play a role in the development of cataplexy. Six patients with severe and persistent cataplexy associated with narcolepsy and 1 patient with "somnambulistic" paralysis were treated with potassium chloride in doses of 30 to 75 grains (2 to 5 Gm.) daily by mouth. All the patients were almost entirely relieved of their cataplectic symptoms, and the patient with somnambulistic paralysis was freed from his attacks. The potassium chloride had no effect on the narcolepsy, which in each case was treated successfully with amphetamine. Determinations of the potassium and sodium contents of the serum were carried out on all but 1 patient. No distinct abnormality was noted, but in 3 patients there seemed to be a lowering of the potassium level of the serum after therapy was instituted.

CHODOFF, Langley Field, Va.

ELECTRIC SHOCK THERAPY IN THE PSYCHOSES. JOSEPH EPSTEIN, J. Nerv. & Ment. Dis. **98**:115 (Aug.) 1943.

Epstein conceives of the electric shock as a mass irritation or stimulation of the cerebrum, the intensity of the reaction being proportionate to the amount and force of the current. The manifestations of such a stimulus are mental, motor and autonomic, with a convulsion marking the maximum reaction. With these phenomena as criteria, he employs a scale of graded reactions to the stimulus, ranging from 1 plus, indicating the mildest petit mal response, to 4 double plus, indicating a severe convulsion with prolonged apnea.

In the 1 plus petit mal reaction the pupils remain unchanged in size and react promptly to light, with little, or no, variation in the pulse rate. The severe petit mal, or subconvulsive, 3 plus, reaction, is marked by temporary rigidity and rolling of the eyes and by pronounced alterations in the pulse rate.

The grand mal seizure, the 4 plus or 4 double plus reaction, is characterized by a definite convulsion with tonic, clonic and apneic phases, dilatation and rigidity of the pupils and either a precipitous rise or fall in pulse rate or a mixed response. In some instances complete cardiac standstill, with a fall in blood pressure occurs. Grand mal seizures in which apnea lasts for five seconds or more beyond the termination of the convulsion are classified as 4 double plus.

The complications of electric shock are similar to those which occur with metrazol shock. However, the technic of arching the patient's back and holding him down minimizes the risk of vertebral fracture, while dislocation of the jaw seems to occur less frequently.

The treatment was administered to 100 patients. There was a recovery rate of 47.2 per cent for the patients with manic-depressive and involutional psychoses, while only 16.2 per cent of the schizophrenic patients recovered. It was felt that although the full convulsion provided the best results, 3 plus, or severe petit mal, reactions were satisfactory in certain cases.

CHODOFF, Langley Field, Va.

THE KENNY VERSUS THE ORTHODOX TREATMENT OF ANTERIOR POLIOMYELITIS. J. ALBERT KEY, Surgery **14**:20, 1943.

The outstanding difference between the Kenny and the orthodox treatment of poliomyelitis may be stated as follows: In the acute febrile stage Sister Kenny

advises active treatment with hot fomentations for relief of muscle spasm, and with the orthodox technic absolute rest and quiet are ordered. The Kenny method avoids the use of casts or splints and begins active muscle reeducation before pain and tenderness have subsided. The author presents evidence to show that this practice has aggravated and prolonged pain and tenderness. The advocates of the Kenny method believe that braces or splints interfere seriously with circulation and cause hopeless muscular atrophy and stiffness. The author states that this does not occur if these aids are properly applied and counters with the statement that the Kenny method causes more extensive atrophy and stiffness than the orthodox treatment in that the patient is kept flat on the back for six months or longer and is turned for treatment only for one hour daily. This is more complete and longer immobilization than is advocated under the orthodox regimen. The tendency of muscles to contract (muscle spasm) subsides when the pain and tenderness disappear, and if deformities are prevented, the symptoms of spasm contractures rarely constitute an important problem under orthodox treatment. The hot packs may cause furuncles and burns, and manipulations of the Kenny method do not prevent the stretching of paralyzed muscles.

An evaluation of the results of the orthodox treatment in a series of cases of poliomyelitis, in accordance with the criteria by which the Kenny method is judged, reveals that the rate of recovery with the use of orthodox methods was as high as that with the Kenny technic, or higher. The author points out that cure is obtained under orthodox methods with far less cost, less risk to life, less time and less labor.

SHENKIN, Philadelphia.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

HAROLD D. PALMER, M.D., *President, in the Chair*

Regular Meeting, Oct. 15, 1943

Neuropsychiatry in War. DR. EDWARD A. STRECKER.

The incidence of neuropsychiatric disabilities in World War II appears to be considerably greater than that in World War I and is of real economic significance. This war has not produced any new psychotic or psychoneurotic entity; rather, the same disorders with which psychiatrists are familiar, intensely colored by their being the result of war, are encountered. The basic conflict appears to be between the instinct of self preservation and soldierly ideals and discipline, a conflict which operates unconsciously under conditions of danger and combat. A pathologic solution of this conflict takes the clinical form of one of the war neuroses. The precipitating factors are fatigue, exhaustion, unbelievable hardship, deprivation and horror. The type of neurosis is determined by the innate personality of the man who breaks.

There is relatively little conversion hysteria in this war. The typical war neuroses are anxiety reactions. Of particular interest are combat fatigue, catastrophic nightmare and the startle reaction.

The prognosis is in direct relation to the patient's previous personality. A well integrated personality stands up best under the conditions of war and responds best to treatment. Men who undergo somatic exhaustion recover promptly. Acute emotional reactions resulting from battle experience respond well to rest, food and simple psychotherapy. Combat fatigue, symptoms of catastrophic nightmare and the startle reaction require longer treatment. The closer to the place where he sustained his disabilities the patient is treated, the better are his chances for restoration.

The most important single element in treatment is physical rest, supplemented by good food. The simplest psychotherapy is used, such as suggestion, reassurance and desensitizing and explanatory treatments. Of the special technics, narcosis therapy and group treatment are effective.

From the standpoint of prevention, adequate screening at induction centers is important. Once the man is in the service, the greatest preventive is morale.

Psychiatry in the Field of Aviation Medicine. COMMANDER E. L. CAVENY (MC), U.S.N.

There is no place in medicine where a thorough knowledge of psychiatry assumes a more significant role than in the successful practice of aviation medicine, especially under the stress and strain of combat operations. Even though the problems are basically and dynamically the same as those encountered in the other branches of the service, there remains a distinct difference. Therefore, whenever possible, the responsibility for the prognosis of psychiatric conditions arising among the flying personnel and the disposition of patients should be assumed by the psychiatrists in the field of aviation medicine. The reaction types most frequently seen were the anxieties and the depressions, especially the latter. No frank psychosis or severe reactive mechanism of any kind was encountered. The character of aviation training usually uncovers at an early stage any predisposing factors to latent psychoneurosis.

Anxiety is a normal accompaniment of any one's reaction on entering conditions of known danger. It is the extensiveness of this anxiety and its persistence after removal of the patient from the known danger in which the psychiatrist is particularly interested. Cases of the "neuroses of war" among the flying personnel are relatively few as compared with their incidence in other branches of the service. There are numerous reasons for this difference, the most important being the work of the flight surgeon, who is especially trained for his work with flying personnel.

Aviation medicine has been practicing "psychoprophylactic" medicine for years. Each person has a limit of endurance for trauma. Once that limit is exceeded, the disabling, incapacitating symptoms automatically appear. The primary duty of the flight surgeon is to prevent the flying personnel from reaching that limit by being continually on the alert for forewarning signs and symptoms. If fatigue and exhaustion are allowed to run on, they will pass into the realms of the neuroses and then require specialized therapy, which means the loss of an aviator. The mission of the aviation division of the Medical Corps of the Navy might be briefly stated: "To keep as many aviators in as many planes in as many flights as possible."

Psychiatric Problems in Military Service. LIEUTENANT COLONEL HENRY A. COTTON.

This paper was not released for publication by the War Department.

DISCUSSION ON PAPERS BY DR. STRECKER, COMMANDER CAVENY AND LIEUTENANT COLONEL COTTON

COMMANDER J. L. MCCARTNEY (MC), U.S.N.R.: These papers are thoroughly interesting. As is generally known, the United States Naval Hospital in Philadelphia is also a veterans' hospital. It takes care of the veterans of this area, including a large number with psychiatric disturbances. It is public information that 1,600,000 men have already been discharged from the services, potential pensioners, since the attack at Pearl Harbor. Six thousand disability applications are already awaiting evaluation from this area alone, of which over 2,600 are concerned with neuropsychiatric disability.

As has been emphasized, the screening process has not been as thorough as it should have been. The facilities for psychiatric care are also far from adequate. At present, in the veterans' outpatient clinic, in the hospital in which all cases are evaluated, from 10 to 20 patients with neuropsychiatric disorders are seen each day. One Navy psychiatrist is doing it all at present. Besides that, patients in the wards must be cared for. There is a problem ahead.

DR. D. J. MCCARTHY: Nothing new in psychiatry came out of the last war. Physicians who were trained fundamentally as neurologists and psychiatrists found that the cases were not complicated.

This war has produced an entirely new type. In the South Seas tropical diseases complicate the neuropsychiatric disorders. I have felt for years that there is a definite level at which symptoms will appear, depending on nervous function and nervous reserve. Exhaustion is brought about by loss of sleep, excessive loss of fluid by perspiration and the tension of anticipation and anxiety. The point at which the exhausted person will show symptoms depends on his integrity. To the full exhaustion will be added nervous symptoms. There may be persistent organic symptoms. These factors must be considered in cases of tropical exhaustion.

The new factors that appear in neuropsychiatric cases will be among the air personnel, with whom an entirely new element of exhaustion enters.

DR. EDWARD A. STRECKER: In placing the hospital stations for the Navy, a long time had to be spent in pouring over maps for islands not infected with malaria and dysentery. More than half the cases of neuroses are complicated by the presence of tropical disease.

I should like to express my appreciation of the splendid papers presented. I have a little personal pride in Dr. Caveny's presentation because he is one of our students; he is leaving in a few days, and his tremendously important experiences have made him available for any place in psychiatry. He has one trait in common with the merchant seaman; nothing will satisfy him except to go back into combat.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

WILLIAM G. LENNOX, M.D., *Presiding*

Regular Meeting, Oct. 20, 1943

Anatomicoclinical Report of a Case of Carbon Monoxide Poisoning, with Survival for Forty-Nine Years; Correlation of Evolution of Extrapyramidal Symptoms and Structural Organization of Motor Pathways of the Forebrain.

DR. PAUL I. YAKOVLEV, Waverley, Mass.

REPORT OF CASE

Clinical History.—A man aged 21 was asphyxiated with carbon monoxide. Prior to the accident he was well and was regularly employed as a piano tuner. After the accident he became mentally impaired and incapable of employment. At the age of 27 he was admitted to a psychiatric institution and remained there for forty-three years. The institution's records permit a reconstruction of the general pattern of his illness.

Up to the age of about 57 he was said to be somewhat deteriorated, but of a pleasant and sociable disposition. He was fond of movies and theatricals, attended field games and read newspapers and books. It was said that he was "able bodied but lame" and that he was "clever manually but odd and peculiar in his ways." Apparently, ever since his admission, he had had an impediment in gait which was described thus: "He used to have hesitancy in starting to move; he would hesitate and 'shimmy'—take a few short steps before going off with motion. He would 'hold everything' because he could not start 'navigating'; he was like Austin S. (Austin was a patient with advanced paralysis agitans)." Withal, he possessed a fair measure of mental and physical faculties, helped in the wards, swept floors, worked on the grounds and in the fields and played the piano "by ear" at the patients' dances. The record indicates that from the age of about 60 progressive mental and physical deterioration began. He became less sociable and was irritable and often seclusive and inaccessible. He apparently had vague, unsystematized paranoid delusions and often refused food. Speech became increasingly repetitive and stereotyped. There were "peculiar twitching movements in his face and arms while he spoke." The "hesitancy" in gait became more pronounced. Eventually, in the last period of his life, about three years before his death, he lost all spontaneity in and initiative for walking and grew more and more bedfast. About a year before his death he became bedridden and incontinent. Six months before his death his condition was as follows: The facies was void of expression. He lay on his back with the head held rigidly up and off the pillow. The entire musculature was in a state of severe and diffuse rigidity. When an attempt was made to put him on his feet by propping him under the shoulders, his body acted as one piece, as rigid as a board. He did not stand if left alone and fell like a log if not supported. When he was pulled forward, he made a few quick, short steps, hardly an inch (2.5 cm.) each, shuffling his feet with tremor-like, jerking movements. When he turned toward the bed, he shuffled and stumbled toward it with surprising increase in locomotive efficiency; yet on reaching the bed he fell on it face down and had to be helped in. The rigidity in passive motions was much greater than would be expected from the observation of spontaneous movements of the extremities. It was greatly increased by his anticipation of being approached, spoken to or moved. It consisted of anticipatory resistance to all passive manipulations of the extremities. His whole body would become taut, as though frozen. The rigidity was a changing one, suddenly yielding to a passive motion at one moment and as suddenly fixing the limb in a new posture at another. It was diffuse, the flexors and the extensors being equally affected. The trunk and the proximal muscles of the extremities were most involved. It was more pronounced on the left side than on the right and was distinctly greater in the lower extremities than in the upper. Except for occasional bouts of pill-rolling movements in the fingers of the right hand, there was no tremor. Occasionally the patient whispered or mumbled inarticulate, repetitive syllables. The tendon reflexes were all present: they were abrupt and were blocked by the rigidity. The plantar reflex was of flexor type. On the basis of the clinical picture, a diagnosis of the syndrome of pallidal rigidity was made. The patient died of bronchopneumonia, at the age of 70.

Pathologic Changes in the Brain.—The weight of the brain was 1,090 Gm. The cerebral hemispheres showed moderate but distinct atrophy of the convolutions. The basal blood vessels were moderately sclerosed. Serial sections of the brain showed simple atrophy of the cerebral cortex, especially in the motor, premotor and frontal areas. In area 4, the Betz cells were unmistakably reduced in number, and many of the remaining ones were shrunken. The entire cortex in this area, as well as in the anteriorly lying areas, was thin. Horizontal sections through the hemispheres revealed old, symmetric cystic areas of softening, strictly confined to the pallidum and destroying on the left side the entire rostroventral half of the nucleus and on the right, where the cyst was smaller, chiefly the rostrodorsal half. The ansa lenticularis was conspicuously demyelinated. Diffuse demyelination was present, also, in the lateral hypothalamic and the subthalamic regions

and in the tegmentum of the midbrain. The red nucleus was pale. The substantia nigra was also atrophied and showed loss of cells and gliosis. The remaining cells were deformed; many were vacuolated and had lost their pigment, much of which was scattered free between cells. The cerebral peduncles were atrophic and shrunken, especially on the right. The bulbar pyramids were shrunken. The spinal cord did not show abnormalities except for some shrinkage and acute, probably terminal, swelling of cells in the anterior horns, especially in the cervical region.

COMMENT

Motor disturbances, considered together under the general term extrapyramidal diseases, or diseases of the basal ganglia, have three outstanding traits in common: (1) frequent dissociation in time between the occurrence of the cerebral lesion and the development of manifest motor disturbances; (2) frequent and paradoxic evanescence of the motor disturbances under the influence of certain emotional affective states, and (3) almost constant impingement of these motor disturbances onto the sphere of the motor expression of personality. Paralysis agitans, Wilson's hepatolenticular degeneration, Huntington's and Sydenham's chorea, hemiballismus, torsion spasm and so-called spastic torticollis, all show these traits. Certain features of the structural organization of the forebrain permit, I believe, a pertinent correlation of these clinical traits and the pathologic changes in the case just reported and in many similar cases of striopallidal lesions with long survival.

The thalamus is a great association and correlation center of the forebrain interpolated between the nuclei of termination of all the afferent root fibers and the pallidum, striatum and cerebral cortex. From the thalamus the fiber systems project on the pallidum directly, via the inferointernal peduncle, and indirectly, via the striatum (thalamostriopallidal relay) and the cortex (thalamocortical and corticostriopallidal and corticopallidal fibers). Thus, the pallidum is a common recipient of impulses from all these centers, and from many others not mentioned here. As such a recipient, the pallidum serves as a head ganglion for the phylogenetically old common path of the forebrain—the ansa lenticularis. Through this great efferent path the impulses are relayed from the forebrain to the subthalamic tegmentum (corpus Luysi, the red nucleus and the substantia nigra) and thence, chiefly via the reticular formation (rubroreticular, reticulospinal, rubrospinal and other descending systems), to the final common path, i. e., to the anterior horn cells and its homologues. Taken as a whole, this system of multiple, usually short, repeatedly overlapping neurons, represents specifically the "extrapyramidal," or "old," motor system of Wilson. As one may readily perceive, it is essentially a "polyneuronic" system, with a huge, combined synaptic surface interpolated on the path of impulses from the cerebral cortex to the effector organs (muscle). From this old motor system the newer motor systems gradually differentiated in the course of phylogenetic development. They did so in a characteristic way. Indeed, from the lower vertebrates to the primates and man, there is observed a tendency to establishment of ever more direct fiber tracts from the most encephalized levels of the nervous system (the cerebral cortex) to the effector organ. These newer, and more direct, connections constantly tend to overlap and by-pass an ever greater number of links in the old (polyneuronic) motor system. For example, the strionigral, the strioluysian and the striorubral fibers by-pass the pallidum and the system of the ansa lenticularis by conveying a quota of impulses from the striatum directly to the subthalamic tegmentum and the reticular formation. As one ascends in the series of vertebrates, one observes that these fiber systems are, in their turn, overlapped by the corticonigral, the corticorubral and the corticoluysian fibers, by-passing the multiple links of the corticostriatal, the striopallidal and the pallidosubthalamic pathways. These, more direct, connections are, in their turn, by-passed by corticotegmental and corticoreticular fibers, which are still more direct; finally, the corticobulbar and corticospinal (pyramidal) fibers by-pass them all and bring the highly selective cortical activity directly on the "firing line" of the final common path to the effector organ. Among the more recent motor systems, of varying degrees of newness, the pyramidal system, the newest of them all, is essentially an "oligoneuronic" system of few relays, representing (in contrast to the old polyneuronic extrapyramidal system) a relatively small, combined synaptic surface interpolated between the cortex and the effector organ. In view of these differences in structural organization of the "old" and the "new" efferent systems of the forebrain, it is conceivable that a lesion of the pallidum, or of any other link in the long chain of the so-called extrapyramidal motor system, may not necessarily lead to immediate and gross disturbances in the sphere of movement so long as there are still available more direct pathways between the forebrain and the final common path. However, if the latter become impaired as a result of a disease or of simple involutive regression, the characteristic syndrome of pallidal rigidity and other disturbances in the sphere of motor behavior may rapidly develop. This, I believe, is what happened in the case just presented.

DISCUSSION

DR. STANLEY COBB: This paper was extraordinarily well presented and extremely interesting. It is rare to have a life history presented so vividly.

The main issue is the relation of cortical areas 4 and 6 and the striatum and their influence on the emotional expression (I prefer the term "emotional expression" rather than "personality"). All know patients who have severe paralysis agitans and who lack emotional expression but who have held on to their intellectual personality extraordinarily well. I agree that the emotional expression is impaired in persons who have lesions of the striatum.

There is confusion in the literature with regard to the use of the word "striatum." In the old textbooks of anatomy the striatum included the pallidum. It is only recently that neurologists have spoken of the pallidum and the striatum as though they were distinct. I prefer Wilson's concept of the new and the old motor system.

I should like to ask Dr. Yakovlev whether he looked for lesions in area 6. It would seem that in the last years of his life the patient lost this area and that this knocked out "the last leg he had to stand on," with resulting increase in motor symptoms.

At autopsy I have seen lesions in the region of the pallidum without clinical evidence of motor deficiencies. The study of this case helps me to understand instances of this kind.

DR. ABRAHAM MYERSON: I should like to ask Dr. Yakovlev whether he is certain that in Sydenham's chorea, the familiar chorea minor, the three principles which he states operate in all types of disorders of the pyramidal tract are present. I doubt whether the child

with Sydenham's chorea has much change in personality. There is not much change in the method of expression. I agree that his principles may apply to paralysis agitans and to other disorders of the extrapyramidal system, but not to chorea minor.

DR. AUGUSTUS S. ROSE: I should like to ask two questions: First, does Dr. Yakovlev believe that catatonia is a functional disorder of the extrapyramidal system? Second, if it is his concept that this patient had a latent striatal disease, made evident clinically by the changes of age and the associated loss of pyramidal cells, how does he explain the cases of paralysis agitans in which hemiplegia produces a "cure"? Signs of paralysis agitans disappear on the hemiplegic side after cerebral infarction. It has always been my idea that some features of paralysis agitans are expressed through the corticospinal pathways.

DR. PAUL I. YAKOVLEV, Waverley, Mass.: I am grateful to Dr. Cobb for raising a point which deserves emphasis. The motor disorders generally attributed to lesions in the basal part of the forebrain are essentially disturbances in the sphere of the motor expression of personality, without necessarily involving the emotional content or the structure of the patient's personality. This is the case with many children who have postencephalitic states and associated behavior disorders, usually described as "personality changes." For example, I remember a girl of 14 with such postencephalitic "personality changes" who had a compulsive, apparently wholly automatic, movement of slapping any one who might be within reach. The prevalent opinion was that she was hysterical and that she did this with deliberate intent and actually derived some vicarious pleasure from the offensive act. Yet she appeared to me to experience an anxiety immediately before and genuine grief after yielding to her compulsive gesture. In fact, she finally tied her right wrist to her belt so that it would not "fly off into people's faces." There were good reasons to doubt that the subjective content of her personality was as much distorted as the manner of its motor expression certainly was.

In regard to the old and the new striatum: Some twenty years ago it was the vogue to speak of the neostriatum and the paleostriatum, meaning respectively the putamen–caudate nucleus complex and the pallidum. Thus, the pallidum became as much a part of the telencephalon as the putamen and the caudate nucleus. However, I came to think of the pallidum as a part of the brain stem (diencephalon), rather than of the cerebral hemisphere. Because of its position mesial to the plane of the choroid fissure and the striothalamic sulcus, its continuity with the substantia nigra and its efferent connections, it belongs to the subthalamic region, from which it appears to have become separated by the passage of fibers of the internal capsule. However, I must admit that this is a controversial matter.

Area 6 was involved in this case. The loss of the larger pyramidal cells in the third layer was especially conspicuous. In my presentation, I emphasized the changes in area 4, simply because the normal structure of this area is familiar to all, and so the alterations there lend themselves well to demonstration on lantern slides. The cortical atrophy was diffuse, especially in areas anterior to the fissure of Rolando. The cortical alterations were those of simple senile atrophy, without areas of softening, old necrosis or severe degeneration. Characteristically, the meninges were fibrosed, yet thin, i. e., in a state of chronic atrophic leptomeningitis, such as is usually seen in cases of simple senile cortical atrophy. There was no hyperplastic thickening of the soft meninges, so characteristic of diffuse degenerative cerebral disease.

In reply to Dr. Myerson's comment concerning Sydenham's (acute) chorea, I must admit that on this point he caught me somewhat "off base," for of all the so-called extrapyramidal motor disorders I have mentioned, acute chorea is least certainly attributable to any specific involvement of the basal ganglia. Little is known about the pathology of Sydenham's chorea. However, I feel that even here the motor disturbances are essentially disturbances of the motor expression of personality, and so may perhaps be included with the disorders under discussion.

Dr. Rose, I do not know whether catatonic rigidity can be attributed to a disorder of the old motor system of the forebrain. The case I have described could have been mistaken for one of the catatonic state. However, pallidal rigidity presents distinctive features. There is no catalepsy. The rigidity consists not only of a "negativistic" resistance to and withdrawal from passive movements, but of a "positivistic" anticipation of such movements, the patient making an inopportune and ineffective attempt to cooperate with the passive motion. The term "paratonic"' rigidity has been applied to this state, to distinguish it from catatonic rigidity. Furthermore, pallidal rigidity often affects one side more than the other, as was the condition in this case, and it is always more conspicuous in the lower extremities than in the upper. Such features are not characteristic of the catatonic state. However, inasmuch as catatonic rigidity and catalepsy can be regarded as postural expressions of an emotional state, it seems not unreasonable that a disorder in the phylogenetically old motor mechanisms of the forebrain may in some way be concerned in their production. They certainly share with other extrapyramidal motor disorders that cardinal trait of evanescence under the influence of certain emotional affective states, and may disappear overnight. As to the statement that paralysis agitans may be cured by hemiplegia, I doubt whether the word "cured" is well chosen. It is true that after a cerebrovascular accident, hemiparesis, with fixed selective contracture may develop in a patient who previously had paralysis agitans, but these new features merely obliterate those of paralysis agitans. Indeed, the lesion of the new, "oligoneuronic" system brings about immediate, relatively fixed symptoms of paralysis, contracture and the Babinski sign. These signs are called objective because they are relatively independent of the emotional affective state of the patient, and so are least dependent on the subjective interpretation of the observer. The symptoms of interruption of these more or less direct fiber tracts from the cerebral cortex to the final common path tend to be spatially limited and are usually confined to a specific category of learned or skilled movements. Not so in the case of the lesions of the old, "polyneuronic" motor system. There is no paralysis, no fixed or selective contracture. The motor abnormalities are dependent on the subjective state of the patient, for they are essentially disturbances of the motor (postural) expression of emotional states. They do not affect directly the movements necessary for achievement, such as the learned movements of manual dexterity, and so there is no paralysis. They affect movements of expression, and so there are rigidities, distortion, incoherence or lack of facial expression or "involuntary" contortions—grotesque posturing movements. That is why these "extrapyramidal" motor disturbances are so arresting to the onlooker and so distressing to the sufferer.

Constitutional Anhedonia and the Social Neurosis.
DR. ABRAHAM MYERSON.

In this paper are presented two conditions, more or less related, in which innate and constitutional or early acquired personality characteristics evolve into a formidable psychopathologic state. The term "constitutional anhedonic personality" is used here to designate a person who from the earliest period of life has shown impairment amounting to serious deficit in the important drives or desires, with a corresponding failure in satisfaction. I have elsewhere described the anhedonic syndrome as part of certain of the neuroses and as a conspicuous feature of the depressive states.

Briefly, the anhedonic syndrome is manifested, first, by the disappearance or impairment of the appetite for food and drink and by failure to experience the corresponding satisfactions. The disability ranges from moderate impairment to complete loss of appetite, and even the substitution for appetite of nausea and vomiting. Second, there is failure in the drive or desire for activity and the corresponding satisfaction. Joy in activity is innate in the human being and manifests itself in all kinds of unorganized forms, but becomes strongly organized into play, sport and work. In the anhedonic state, the desire for activity, as well as the satisfaction derived thereby, is greatly impaired. Third, the appetite or desire for rest and the satisfaction of recuperation are also involved in the anhedonic syndrome. The tired feeling, which is so conspicuous in all the neuroses and the depressive states, may be supplanted by a final absence of the feeling of fatigue, though there is no sense of energy and no desire for or satisfaction in play, sport or work. Sleep becomes greatly impaired, and the desire for sleep, which is expressed by yawning, drowsiness and sleepiness, disappears and is replaced by a restless wakefulness, which is distressing and disorganizing. Fourth, the sexual drives and satisfactions are conspicuously altered in the acquired anhedonic states. This is too well known to need amplification, but it should be stated that impairment in this sphere is only part of a general impairment of desire and satisfaction. Finally, the social desires and satisfaction, which belong indissolubly to the nature of the herd animal known as man, become disorganized, deficient and even destroyed in the anhedonic state. There is no joy in company, though there may be fear of being alone. As all communication with one's fellow men disappears, a sense of being alone and alien on the scene of things becomes paramount, though no delusion formation is present in the anhedonic syndrome as such.

Constitutional anhedonia differs from the acquired anhedonic state in that the patient has shown impairment in all these drives from the earliest days of his life, or, if all the drives have not been deficient, some have been conspicuously impaired or deficient from childhood. Such persons go through life without experiencing real hunger for food. They present feeding problems in childhood and remain without zestful desire or lustful satisfactions from one end of life to the other. Similarly, there is impairment of the drive and desire for activity. As children, such persons have to be forced into playing. They have no desire for activity as such, and, though they may become finally industrious and well organized in activity, it is without enthusiasm and spontaneity. Sexually, they may be entirely continent. Virginity comes easily to them. Masturbation is not common, though it may exist. They go through life wondering why others feel such intense passion, and they may seek to experiment with eroticism, though without success. It is significant that in several of my cases nocturnal emissions have not taken place. In females, frigidity and lack of responsiveness are the rule. The social activities are likewise impaired. In certain persons the incapacity for social relationships may be supplanted by what will later be described as social neurosis, but this does not necessarily occur. Such persons go through life on the periphery of society, finding social communication impossible, but often not feeling any great lack, though they may recognize their deficiency as abnormal and become anxious because of this insight.

It is essential to this theme that it be recognized that society exercises a profound, and often disorganizing, influence on the desires and satisfactions of mankind. The social structure is confusingly ambivalent in its attitudes toward the flesh, that is, toward desire and satisfaction. The curious phenomenon of asceticism has appeared, which denies the validity of the pleasures of existence, and often denounces them as unworthy. Side by side with the anaphrodisiac forces of the social scene are opposing forces, which voice vigorously an excessive hedonism. They may be called aphrodisiac forces. Man is *homo asceticus* and *homo sensualis* at one and the same time, and his desires and satisfactions are barraged by contradictory admonitions and exciting and inhibiting forces, of opposing nature.

The term "constitutional," it must be noted, does not necessarily mean "hereditary." The constitution can be altered by environmental forces operating at an early period of life. "Constitutional" merely indicates the physiologic, psychologic structure of the background, which reacts continuously with the environment and has, on the whole, a definite trend toward a certain type of reaction.

By the term "social neurosis" is meant a group of reactions of adverse type which take place in the person's contact with his fellow man, in the face to face association of human beings. There is a wide variability in ease in social relationships. Some persons find every social contact effortless and respond with power and pleasurable success to the flow of social meetings and partings which make up the pattern of social relations. There are others to whom every human contact means a struggle, which finally disorganizes the visceral functions in general or in focal ways, so that meeting others means to them blushing, flushing, sweating, palpitation, gastrointestinal disturbance, genitourinary difficulty and the whole gamut of visceral overresponse, culminating in feelings of faintness and fears of impending death or insanity. The agony of self consciousness develops into a severe psychosomatic response, which then becomes the center of fearful attention; situation becomes associated with response and phobia, and a neurosis is born. In the endless, vicious circle which this involves, there takes place, finally, anticipation anxiety, all of which starts with a personality difficulty born not essentially of inferiority feelings but of lack of ease in social relationships and which finally becomes a form of the anxiety neurosis, and of anxiety states in general, since it is only a step from the anxiety neurosis to the anxiety psychosis.

The psychologic basis of this cannot be given here. It is born of the fact that all social relationships have to be bridged over by greeting and conventional formulas before social communion takes place, that an innate suspicion of one another is present in the social reactions of human beings, that concealment and revealment of an appropriate nature are part of the technics of successful social adjustment and that ease of com-

munication is a necessity for successful social relations. The person who has acquired the social neurosis feels that his psychosomatic disorder gives him away. He cannot successfully conceal what he feels, nor can he reveal himself as he wishes to be seen and evaluated by his fellows, because ease of communication becomes frozen in the inadequate, halting speech and social act.

It is my opinion that constitutional anhedona leads to many of the forms of psychopathic development and that as an essential part of a psychiatric history, a study of the intensity and direction of all the desires and satisfactions should be made. The social neurosis leads, I believe, in two directions: First, into the anxiety states, and, second, by a transition from fear of one's fellow men and fear of the psychosomatic disorders, into suspicion, somatic delusion and ideas of reference.

DISCUSSION

DR. H. HALE POWERS, Wellesley, Mass.: Dr. Myerson should say a little more about the early history of this case—the early environment and the heredity.

DR. CLEMENS E. BENDA, Wrentham, Mass.: Dr. Myerson has given an extremely interesting description of a neurosis which he calls "social"; I feel, however, that there is a kind of paradox in his concept that the neurosis is due to constitutional factors. The constitutional variations among men are great; there are weak people and powerful people, active natures and passive natures, but the constitutional factors in themselves do not produce a neurosis. It is the reaction of a specific personality to certain environmental factors which is responsible for the neurosis, and not much is gained if one retreats to the position that the constitutional factors represent the main factor in the formation of a neurosis. Regardless of how one regards psychoanalysis, this school has taught a great deal about the importance of experiences in childhood with respect to the development of a neurosis, and this side of the problem should be given more emphasis.

DR. ABRAHAM MYERSON: The patient was of a Russian Jewish immigrant family. He was brought up in the United States. His family was relatively successful—they were small business people. True, they had to struggle and were not far ahead of poverty. The patient was fairly well educated, having gone part way through college. He had a good business training and was a certified public accountant. He was a man of good physique. Apparently, nothing in his early life had conditioned him. He had a reasonably happy family life, with no conflicts in the home. He went to work at the age of 20, studied nights, qualified as a certified public accountant and finally went into business for himself. He earned a good living and was thrifty. He came in to see me about ten years ago, with some degree of anxiety and the question, "Why am I not capable of experiencing what other people experience?" I could not answer the question satisfactorily, but I tried administration of various glandular preparations and drugs; in the main, I tried to increase his desire and appetite by seeking ways of awakening them through increased activity in general—on the basis of the idea that if one sits down to eat, one may get hungry. He continued to be anhedonic.

In one form or another, constitutional anhedonia is not a rare, but a relatively common, situation.

In reply to Dr. Benda, I do not see any paradox. In my opinion, it is a one-sided view of life to think that constitution and environment are distinct. The germ plasm is never out of reach of the environment. The terms "constitution" and "environment" are convenient dichotomies, but, in reality, one cannot contract a disease or sustain an injury unless one has a constitutional predilection to it. Man has the constitutional liability to fracture of the skull when a brick falls on his head; otherwise the brick would be fractured. Though there is the constitutional liability to fracture of the skull, by means of a brick, the brick, nevertheless, has to fall on the head to cause the fracture.

Given the ordinary circumstances of life, the person with constitutional anhedonia does not have the drive other people have under the same circumstances. But the term "constitutional" does not imply hopelessness. Diabetes is constitutional, but it can be well managed. Since "constitutional" and "environmental" are not opposing terms, it is possible by environmental means to change constitution. So employment of drugs, glandular preparations, greater motivation and push methods may help even the patient with constitutional anhedonia.

In my opinion, the social neurosis is one of the most common of the predisposing factors in the production of anxiety states. I believe that the most common general background for the development of severe anxiety states, for neuroses which develop slowly and insidiously and for certain types of dementia precox is the inability of certain persons to meet others freely and easily. A social situation breeds an abnormal response, and the response breeds an anticipatory dread of the situation. The symptoms develop in a vicious circle, which starts with unease, become visceral disorder, then anxiety, retreat and inferiority and may go on to delusion. The delusionary symptoms take place when the disturbance is attributed to other people. The patient then says, "These people are injuring me," instead of, "I cannot meet them." Thus, a neurosis swings directly over to a psychosis.

Book Reviews

The Nature and Treatment of Mental Disorders. By Thomas Verner Moore, O.S.B., Ph.D., M.D. Price, $4. Pp. 312. New York: Grune & Stratton, Inc., 1943.

Dr. Moore, who is a Catholic priest, as well as a psychiatrist, and is professor of psychology and psychiatry at the Catholic University of America, has written a provocative book. In his preface he states:

"The present work is an attempt to make a contribution to our understanding of mental disorders and to illustrate a wide variety of techniques in dealing with the many and varied problems with which the psychiatrist is confronted. . . . We have therefore attempted to outline, criticize and supplement classic theories of psychopathology and to make use of these theories in order to throw light on the nature of mental disorders."

The book is divided into four sections, entitled "Psychopathology," "Therapy by Psychological Analysis," "Miscellaneous Techniques" and "Organic Emotional Disorders."

A considerable portion of the chapters on "psychopathology" deals with the writings of Freud. The works of Jung, Adler and Franz Alexander are described in less detail. Although the author repeatedly mentions Freud's valuable contribution, he is critical of him and states:

"Freud has profoundly influenced the treatment of mental disorders by psychological procedures. His fundamental technique of mental analysis was an important contribution to psychotherapy. But his theoretical interpretations never grow out of a sound statistical procedure and amount to nothing more than suggestions for future scientific investigations."

In discussing Freud's ideas about sexuality, he states:

"A celibate life does not contribute to insanity, as strict Freudian theory would demand."

He then describes his own studies on the incidence of psychoneuroses and psychoses among nuns and priests as compared with that in the general population. He states:

"The percentage of psychoneurotic conditions in first admissions to hospitals for mental disease in the United States in 1933 was 2.1 for men and 4.1 for women, whereas the percentage of psychoneurotic conditions for all priests in mental hospitals in the United States for 1935 was 1.90 and for nuns 2.58. . . . In 1934, the figures for the incidence of insanity per 100,000 of the population by marital classifications were: single, 261.1; married, 158.83; widowed, 330.73; divorced, 745.1. The insanity rate per 100,000 in 1935 was: For all priests, 121.65; for all nuns, 124.40. (In 1935 there were 122,220 nuns and 30,250 priests in the United States.)"

The information for this study was obtained from 100 per cent of the Catholic hospitals for mental diseases, from 96.53 per cent of the state institutions, from 100 per cent of the city hospitals, from 91.04 per cent of the county sanatoriums and from 76.96 per cent of private institutions.

Moore uses the term "analysis" frequently in describing his treatment of patients, but he obviously does not refer to the psychoanalytic procedure as understood by psychiatrists. For example, he describes a patient whom he had seen on only four occasions. She was asked to write out a history of her emotional difficulties. She described an emotional episode in her past life, and while describing it she became pale and anxious. Moore stated that this was a pronouncend "abreaction" and was followed by disappearance of her symptoms. She was subsequently seen on three occasions and had had no further recurrence of her fears; the author then comments:

"Thus, it seems that analysis and reliving a traumatic episode accompanied by intense emotional abreaction, has *de facto* been associated with the disappearance of the neurotic symptoms."

Under the section on "Therapy by Psychological Analysis," Moore describes free association and dream analysis. This technic is used after a patient has been asked to write out a life history, with an account of his emotional conflicts, his trials and the origin of the present illness. The author then adds:

"The next step in treatment [is] analysis by associations developing from words suggested by the patient's history."

In discussing dreams, he states:

"It seems likely that some at least of the dreams presented by a patient deal with the more serious problems of his life at the time, and the interpretation of such dreams is of major importance in psychotherapy. Others may go back to infantile sexuality or be plain wish fulfillment dreams giving an outlet to present drives. Such dreams are of minor importance in psychotherapy."

Other forms of treatment described include "mental therapy by family reorganization," "educational therapy" and "bibliotherapy," and many cases are cited in detail in which the results of these forms of treatment are shown. The author emphasizes the role of religion in the treatment of patients, and he describes how he discusses with patients religious principles and church dogma. He also has a chapter dealing with the pharmacologic treatment of mental disorders and describes his own contribution in the form of eschatin (adrenal cortex extract) and follutein (a preparation containing chorionic gonadotropin) in the treatment respectively of manic-depressive psychoses and schizophrenia.

Moore states that the purpose of his book is to emphasize that one should use whatever is available in psychology or physiology in the diagnosis and treatment of abnormal conditions of the human mind. Although many readers, particularly freudian psychoanalysts, will disagree with much that the author says, the reviewer believes that this book should be accepted in the nature of a psychiatric challenge.

Physiological Psychology. By Clifford T. Morgan, Associate in Psychology, Johns Hopkins University. Price, $4. Pp. 599, plus index. New York: McGraw-Hill Book Company, Inc., 1943.

The author states in his preface that this publication is intended to be both a textbook for undergraduates who are preparing for psychology or medicine and a reference book for graduate workers and students in psychology, physiology and medicine. The volume is divided into twenty-six chapters, beginning with an

historical introduction and a discussion of cellular functions and concluding, in the final chapter, with a consideration of symbolic processes. For practical purposes, however, this work may be considered as having two broad subdivisions: the first, a review of some of the fundamental considerations of general and neural physiology, and, the second, the author's application and extension of this material to an interpretation of the physiologic basis of psychologic phenomena.

The first section surveys logically and coherently some features of general physiology and then proceeds to a discussion of the physiology of the nervous system as a whole, followed by a review of the physiology of the special senses and concluding with a consideration of the physiology of some of the motor functions. The features are brought together under such chapter headings as "the internal environment," "the physiology of nerve cells," "phylogenetic and ontogenetic development," the "chemical senses" and "reflexes and postures."

In his preface, the author states that his twofold purpose of making the book useful both to the undergraduate and to the advanced worker could not be fully attained in the consideration of every phase of physiologic psychology. Therefore, in order to keep the book as factual and as free from speculation and bias as possible, he adopts the principle of emphasizing experimental material obtained from animal studies at the expense of clinical observations on human subjects.

This principle is demonstrably operative in the first section of the book. As a result, one sees developed gradually a mechanistic doctrine, with emphasis on reflexive behavior and the concept of levels of function throughout the nervous system and the interaction of one level of organization on another to give rise to the final behavior pattern.

While in the first part of the book this method of exposition and development serves adequately most (but not all) of the time, in the second portion difficulties immediately become apparent. In his chapter on emotion, for instance, the author states, ". . . little information, unfortunately, is available concerning the mechanics of fear or of unpleasantness." It seems to the reviewer that in any discussion of emotions these elements are rather crucial. In connection with anxiety, the author states: "Anxiety is not simply emotion. It is the anticipation of unpleasant events to occur in the future. To be sure the anxious person may not know what it is he anticipates, but the anxiety nevertheless represents readiness to react to a future situation." The reviewer would raise the question here of what future event a patient had in mind when she said recently, "I don't know what it is, doctor, but I get so nervous and upset whenever I see chicken feathers."

It may be said in summary that in this volume the author is concerned with an attempt to carry over a rather mechanistic, Sherringtonian psychology in a study of mental and emotional function. It is the feeling of this reviewer that an attempt to arrive at an understanding of these processes without the use of contemporary dynamic psychology cannot but fall short. That this purpose can be achieved with a real approach to "objectivity" is illustrated by the animal work of Masserman and others.

The book serves a useful purpose, however, in presenting the close correlation of physiologic function and higher psychologic processes. Psychologic and neurophysiologic material at hand today permits a deeper exploration than the author has seen fit to carry out at this time.

What Is Hypnosis? Studies in Conditioning. By Andrew Salter. Price $2. Pp. 87. New York: Richard R. Smith, 1944.

This book seems to offer little new on hypnosis. In his series of experiments the author suggests certain paralyses, anesthesias and emotional states to persons under hypnosis. He states that he can train a few selected persons to hypnotize themselves by repeating certain suggestions, which he has made, in an automatic fashion. He constantly repeats that hypnosis consists only of conditioned reflexes and that "rapport" is of no importance. This statement is not supported by adequate data. There is only a poor attempt to understand the hypnotic state itself. He confuses hypnosis with the method of induction. Throughout the book one senses the lack of any frame of reference for the understanding of human personality. The volume adds nothing that is new to the technic of hypnosis or suggestion. The conclusions are unscientific, sketchy and unconvincing.